

14

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 March 2006 (16.03.2006)

PCT

(10) International Publication Number
WO 2006/027711 A2

(51) International Patent Classification:
A61K 47148 (2006.01)

(21) International Application Number:

PCT/IB2005/052797

(22) International Filing Date: 26 August 2005 (26.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/604,632	26 August 2004 (26.08.2004)	US
779/MUM/2005	1 July 2005 (01.07.2005)	IN

GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US):
NICHOLAS PIRAMAL INDIA LIMITED [IN/IN];
Nicholas Piramal Research Centre, 1, Nirlon complex
Near NSE complex, (behind the Hub) Goregaon (East),
Mumbai 400 063 (IN).

(71) Applicant and

(72) Inventor: **SATYAM, Apparao** [US/IN]; Nicholas Piramal Research Centre, 1, Nirlon complex Near NSE complex, (behind the Hub) Goregaon (East), Mumbai 400 063 (IN).

(74) Agent: **VEPACHEDU, Sreenivasarao**; Vepachedu Professional Corporation, 1230 Georgetown Way, Vernon Hills, IL 60061 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Ui)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

Published:

- without international search report and to be republished upon receipt of that report
- under Rule 91.1(f), with a request for rectification

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PRODRUGS CONTAINING NOVEL BIO-CLEAVABLE LINKERS

(57) Abstract: The invention provides the compounds of formula (I) or pharmaceutically acceptable salts thereof. The invention also provides pharmaceutical compositions comprising one or more compounds of formula (I) or intermediates thereof and one more of pharmaceutically acceptable carriers, vehicles or diluents. The invention further provides methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula (I).

WO 2006/027711 A2

PRODRUGS CONTAINING NOVEL BIO-CLEAVABLE LINKERS

This application takes priority from US Provisional Application USSN:
60/604,632 filed 26 August 2004 and Indian Provisional Application 779/MUM/2005

5 filed 01 July 2005 and are herein incorporated in their entirety.

Field of the Invention

The present invention relates to compositions of prodrugs, including NO-releasing prodrugs, codrugs, double prodrugs and mutual prodrugs, containing bio-labile linkers and linkages, processes for their preparation and pharmaceutical compositions containing
10 them and their use.

Background of the Invention

A prodrug is an active drug chemically transformed into a *per se* inactive derivative which by virtue of chemical or enzymatic attack is converted to the parent drug within the body before or after reaching the site of action. The process of converting an
15 active drug into inactive form is called drug latention. Prodrugs can be carrier-linked-prodrugs and bioprecursors. The carrier-linked prodrug results from a temporary linkage of the active molecule with a transport moiety. Such prodrugs are less active or inactive compared to the parent active drug. The transport moiety will be chosen for its non-toxicity and its ability to ensure the release of the active principle with efficient kinetics.
20 Whereas the bioprecursors result from a molecular modification of the active principle itself by generation of a new molecule that is capable of being a substrate to the metabolizing enzymes releasing the active principle as a metabolite.

Prodrugs are prepared to alter the drug pharmacokinetics, improve stability and solubility, decrease toxicity, increase specificity, and increase duration of the
25 pharmacological effect of the drug. By altering pharmacokinetics the drug bioavailability is increased by increasing absorption, distribution, biotransformation, and excretion of the drug. Limited intestinal absorption, distribution, fast metabolism, and toxicity are some of the causes of failure of drug candidates during development. Avoidance of the foreseeable or proven pharmacokinetic defects thus assumes considerable significance in
30 drug research. Accordingly, prodrugs play a significant role in drug research as well.

In designing the prodrugs, it is important to consider the following factors: a) the linkage between the carrier and the drug is usually a covalent bond, b) the prodrug is inactive or less active than the active principle, c) the prodrug synthesis should not be expensive, d) the prodrug has to be reversible or bioreversible derivative of the drug, and
5 e) the carrier moiety must be non-toxic and inactive when released.

Prodrugs are usually prepared by: a) formation of ester, hemiesters, carbonate esters, nitrate esters, amides, hydroxamic acids, carbamates, imines, mannich bases, and enamines of the active drug, b) functionalizing the drug with azo, glycoside, peptide, and ether functional groups, c) use of polymers, salts, complexes, phosphoramides, acetals,
10 hemiacetals, and ketal forms of the drug. For example, see Andrejus Korolkovas's, "Essentials of Medicinal Chemistry", pp. 97-118.

The discovery and characterization of endothelium-derived nitric oxide (NO) was the subject of the 1998 Nobel Prize in Medicine and Physiology. NO is a major signaling molecule with important biological roles. See, for example, Kerwin, Jr., J. F. et al., J.
15 Med. Chem. 1995, 38, 4343, and Williams, R. J. P., Chem. Soc. Rev., 1996, 77. The major biological functions of NO include controlling blood pressure, smoothing muscle tone and inhibition of platelet adherence and aggregation, assisting the immune system in destroying tumor cells and intracellular pathogens and participating in neuronal synaptic transmission. See, for example, Moncada, S. et al., Pharmacol. Rev. 1991, 43, 109; Bredt,
20 D.S. et al., Annu. Rev. Biochem., 1994, 63, 175; Schmidt, H. H. W. et al., Cell 1994, 78, 919; Feldman, P. L. et al., Chem. and Eng. News. 1993, 71 (20th December issue), 26; and Wilsonm E. K., Chem. and Eng. News. 2004 (8th March issue), 39. Endogenously, NO is produced from arginine by the catalytic action of nitric oxide synthase. See, for example, Nathan, C. et al., Cell 1994, 78, 915, and Marietta, M. A., Cell 1994, 78, 927.

25 NO is a free radical as well as a scavenger of free radicals. NO reacts quickly with ubiquitously generated reactive oxygen species (ROS) such as superoxide (O_2^-) to generate a nefarious peroxynitrite ($ONOO^-$) molecule, which is implicated in many human diseases such as diabetes, heart disease, Alzheimer's disease and multiple sclerosis. In this setting, NO is often viewed as pathogenic. However, the chemistry of
30 NO can also be a significant factor in lessening the injury mediated by reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS). There is a relationship

between NO and oxidation, nitrosation and nitration reactions. A number of factors determine whether NO promotes, abates or interconnects these chemistries. See, for example, Espay, et al., A chemical perspective on the interplay between NO, reactive oxygen species, and reactive nitrogen oxide species, Ann N. Y. Acad. Sci. 2002, 962, 5 195.

Thus, by being a free radical, along with the ability to scavenge other free radicals, NO is placed in a pivotal regulatory position. Insight into these pathophysiological processes and signaling are highly relevant to develop therapeutics.

NO deficiency has been implicated in the genesis and evolution of several disease states. In patients with cardiovascular problems, the production of superoxide is increased and level or location of NO synthesis is disrupted thereby causing cellular dysfunction as a result of vasoconstriction of blood vessels, which can lead to, if prolonged, cell damage or death. Agents that act to maintain the normal balance between NO and superoxide in vascular endothelial cells may prove particularly useful in this regard. See, for example, 10 Stokes, K., et al., Free Radic. Bio. Med., 2002, 33, 1026-1036.

Nutritional and pharmacological therapies that enhance the bioactivity or production of NO have been shown to improve endothelium-dependent vasodilation, reduce symptoms, and slow the progression of atherosclerosis. Some of the strategies for NO modulation encompass anti-inflammatory, sexual dysfunction, and cardiovascular 20 indications. Apart from newly developed drugs, several commonly used cardiovascular drugs exert their beneficial action, at least in part, by modulating the NO pathway. Pharmacological compounds that release NO have been useful tools for evaluating the pivotal role of NO in cardiovascular physiology and therapeutics.

NO-DONORS:

25 There are a wide variety of structurally dissimilar organic compounds that act as NO donors and release NO in solution. Some NO donors, such as isoamyl nitrite, nitroglycerine (GTN) and sodium nitroprusside, have been used in cardiovascular medicine long before their biochemical mechanism was understood. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle 30 through activation of guanylate cyclase with subsequent formation of cGMP. The relative importance of enzymatic versus non-enzymatic pathways for NO release, the identity of

the actual NO-generating enzymes and the existence of competing metabolic events are additional important determinants of the different NO donor classes. Pharmacological compounds that release NO constitute two broad classes of compounds: those that release NO or one of its redox congeners spontaneously and those that require enzymatic metabolism to generate NO. See, for example, Ignarro, L. J. et al., Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview, *Circ. Res.* 2002, 90, 21-28.

Nitroglycerine/glycerine trinitrate (GTN) and compounds referred to as nitrovasodilators or NO donors are frequently used in the treatment of ischemic heart disease. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through activation of guanylate cyclase with subsequent formation of cGMP. However, early development of tolerance to nitrate therapy, particularly during acute myocardial infarction, has been the clinically significant drawback with GTN and some of the other available organic nitrates. This is a significant clinical problem and there exists a need for novel nitrate-based anti-anginal agents, which do not cause the problem of nitrate tolerance.

There are a number of new examples of organic nitrates in which an alkyl or aralkyl mononitrate is covalently linked to an existing drug molecule. Existing drugs from a large number of therapeutic areas such as anti-inflammatory, antiallergic, antibiotic, anticancer, antidiabetic, antiviral, antihypertensive, antianginal, anticonvulsant, analgesic, antiasthmatic, antidepressant, antidiarrheal, antiinfective, antimigraine, antipsychotic, antipyretic, antiulcerative, antithrombotic, etc., were made and evaluated. Some of Nicox's patents include: Synthesis and evaluation of nitrooxy derivatives of NSAIDs (WO 9412463, WO 0230867, WO 0292072, WO 0313499 and WO 0384550), aspirin (WO 9716405, WO 0044705 and WO 0104082), paracetamol (WO 0112584 and WO 0230866), antiepileptic agents (WO 0300642 and WO 0300643), COX-2 inhibitors (WO 0400781 and WO 0400300), statins (WO 04105754), ACE inhibitors (WO 041 10432 and WO 04106300), and of known drugs used for the treatment of disease conditions resulting from oxidative stress and endothelial dysfunction (WO 0061537).

Most of these nitrate esters were shown to possess not only superior or equal efficacy when compared to the original drug but also exhibit much-reduced side effects. In fact, because of their superior efficacy combined with reduced toxicity, a few of such nitrate ester-containing drug conjugates are successfully passing through various stages of clinical trials. Some of Nicox's nitrooxy derivatives of drugs which are in clinical trials include: NCX 4016 (Phase II, peripheral vascular diseases), NCX 701 (Phase II, Acute pain), HCT 1026 (Phase I, Alzheimer's disease), HCT 3012 (Phase II, Osteoarthritis), NCX 285 (IND, Osteoarthritis), NCX 1022 (Phase Ha completed, Dermatitis), NCX 1020 (Phase I, Asthma/COPD), NCX 1000 (Phase I, Portal hypertension), and NCX 1510 (Phase II, Allergic rhinitis).

US5767134 and US20050002942A1 disclosed a few disulfide-containing prodrugs/folate-drug conjugates. WO 9842661, US 5807847, WO 0054756 and WO 0149275 reported a few nitrooxy derivatives of organic molecules containing sulfahydryl or disulfide group which are called "SS-nitrates". These references are incorporated herein by reference.

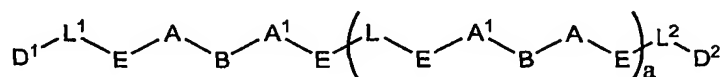
Representative examples from WO 9842661 have shown superior vasorelaxant activity and no tolerance was observed to the cGMP-increasing effects of those compounds under the same experimental conditions used for the induction of in vivo tolerance. WO 0149275 reports drug conjugates where an anti-inflammatory drug is covalently linked to the *bet* α -mercapto-nitrate via thioester bond. Biotransformation pathways proposed for NO release from GTN have largely been heme-dependent or sulfahydryl-dependent. See, for examples, Thatcher, G. R. J. et al., Chem.Soc. Rev. 1998, 27, 331 and reference cited therein, and Bennett, B M. et al., Trends Pharmacol, Sci. 1994, 15, 245. These references are incorporated herein by reference.

A mutual prodrug is the association in a unique molecule of two drugs, usually synergistic, attached to each other, one drug being the carrier for the other and vice versa. The embodiments of the invention also provide mutual prodrugs, which are prodrugs of two or three therapeutic agents currently used/potential for use in combination therapy utilizing novel bio-cleavable linkers, water-soluble prodrugs of insoluble/sparingly-soluble therapeutic agents using the same linker technology and water-soluble double and

triple prodrugs of sparingly-soluble therapeutic agents or any of the prodrugs linked to NO-releasing agent using the same linker technology.

Summary of the Invention

Present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof:



Formula (I)

wherein,

10 a is 0-2;

B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_c$, S-S, S-S=O, S-SO₂ or S-S=NH;

b is 1-6; c is 1-1000;

A and A¹ independently represent a bond, $(CH_2)_a$, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

15 d is 1-8;

D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -

OC(=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R⁴CC=O)NHR¹ and -N(R⁴SO₂NHR¹;

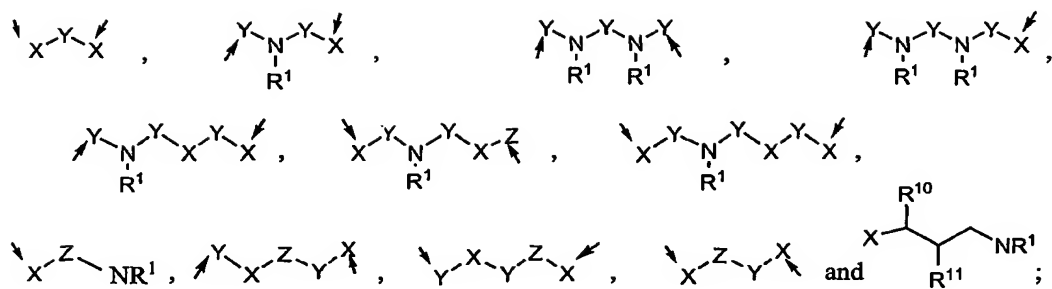
D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³,

20 R⁴, NO, NO₂, a linkable nitric oxide-releasing group comprising a NONOate, a group comprising one or more of water-solubilizing functional groups, or a polymer;

E independently represents CH₂ or a bond;

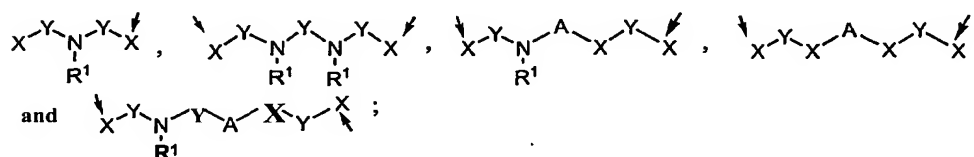
L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:

25



L is R^{12} or a group with bonding in any direction, independently selected from the group consisting of:

5



X independently represents a bond, C, O, S, or NR^1 ;

Y independently represents a bond, C=O, C=S, S=O, SO_2 , PC(=O)XR^1 , or $(\text{CH}_2)_a$;

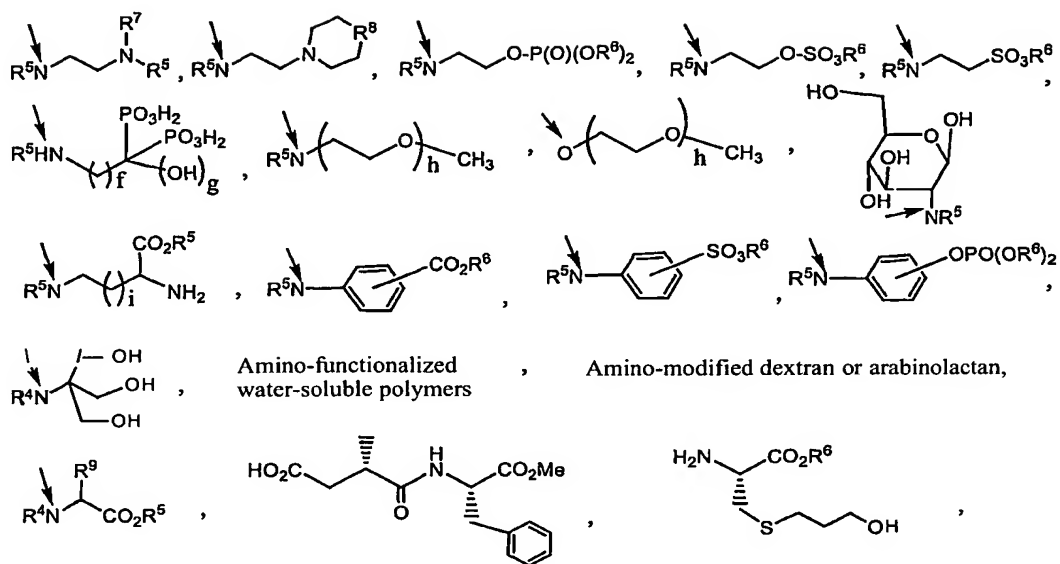
Z independently represents a bond, or $(\text{CH}_2)_j$; wherein, j is 1-4;

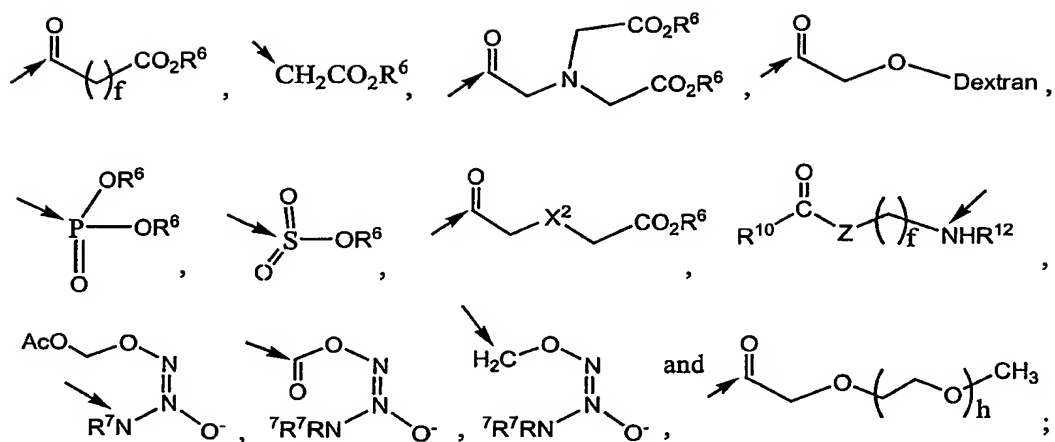
10 R^1 independently represents a bond, H, $(\text{C}_1\text{-Cs})$ alkyl, $(\text{Cs-Cu})\text{SiYI}$, aralkyl or M^{6+} ;

R^2 independently represents H, NH_2 , or NHAc ;

R^3 independently represents H, CO_2R^5 , $\text{CH}_2\text{CO}_2\text{R}^5$,

R^4 independently represents H, OH, 0-(Ci-C)_j alkyl, 0 M^{6+} , or a group selected from the group consisting of:

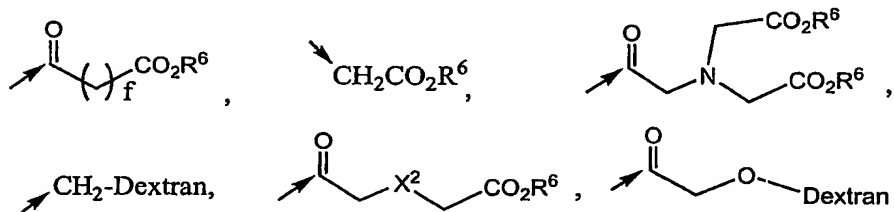




M independently represents Na, K or a pharmaceutically acceptable metal ion,

5 e = 1-3,

R^5 independently represents at each occurrence H, M^{e+} , (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, substituted (C₅-C₁₄)aryl, hetero(C₂-C₁₄)aryl, C(=O)(CH₂)_fCHR⁹CO₂R⁵; CH₂C(=O)OR⁵, P(=O)(OR⁵)₂,



X^2 independently represents O, S, SO, SO_2 , or NR^5 ;

R^6 independently represents H, Na^+ , K^+ , any other pharmaceutically acceptable metal ion, (Ci- C_8)alkyl, or (C_3 - C_8)cycloalkyl,

R^7 independently represents at each occurrence same or different R^5 ;

5 R^8 independently represents CH_2 , O, NR^4 , S, S=O or O=S=O;

R^9 independently represents H, (Ci- C_8)alkyl or an amino acid;

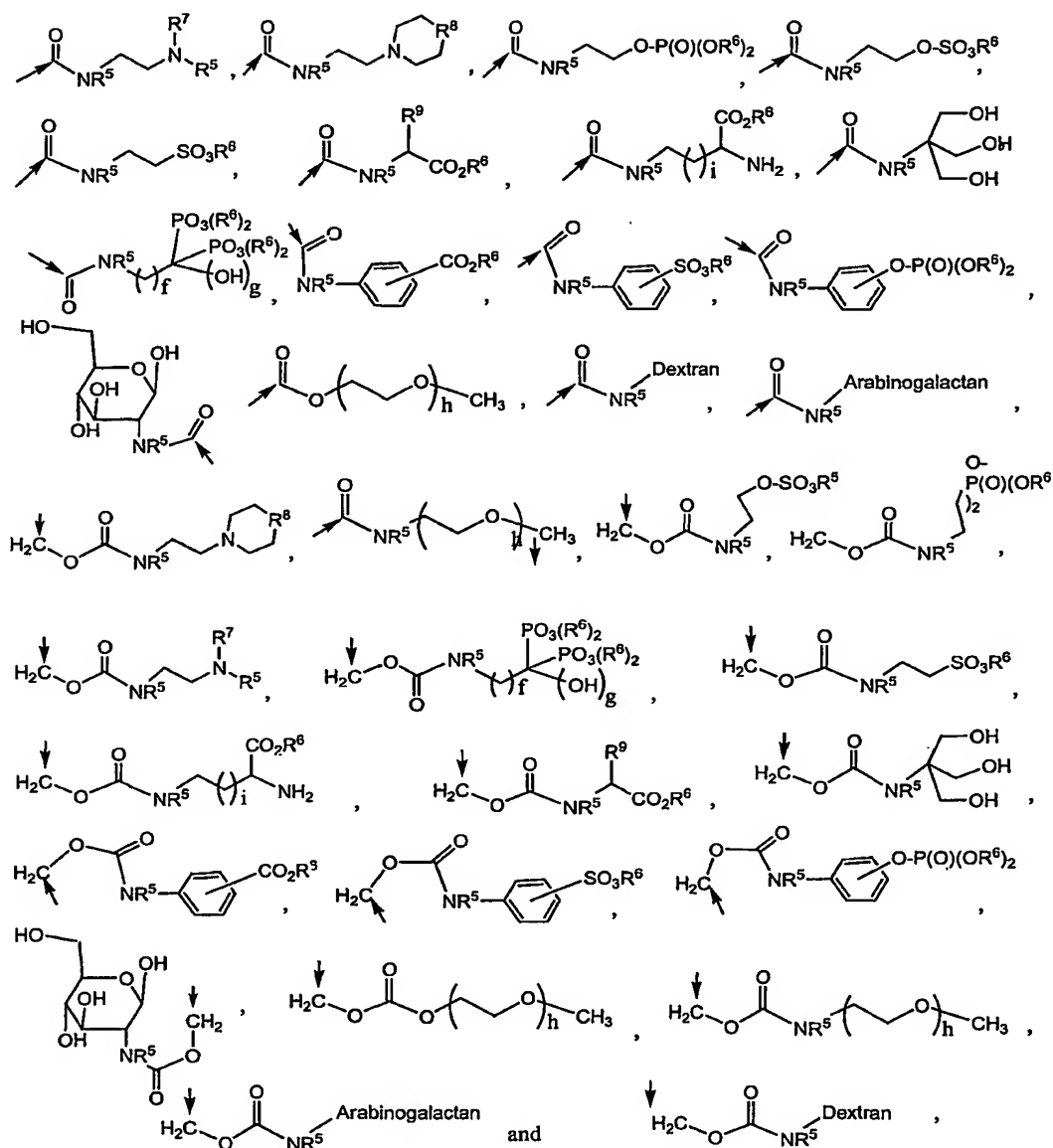
f is 0-6;

g is 0-1;

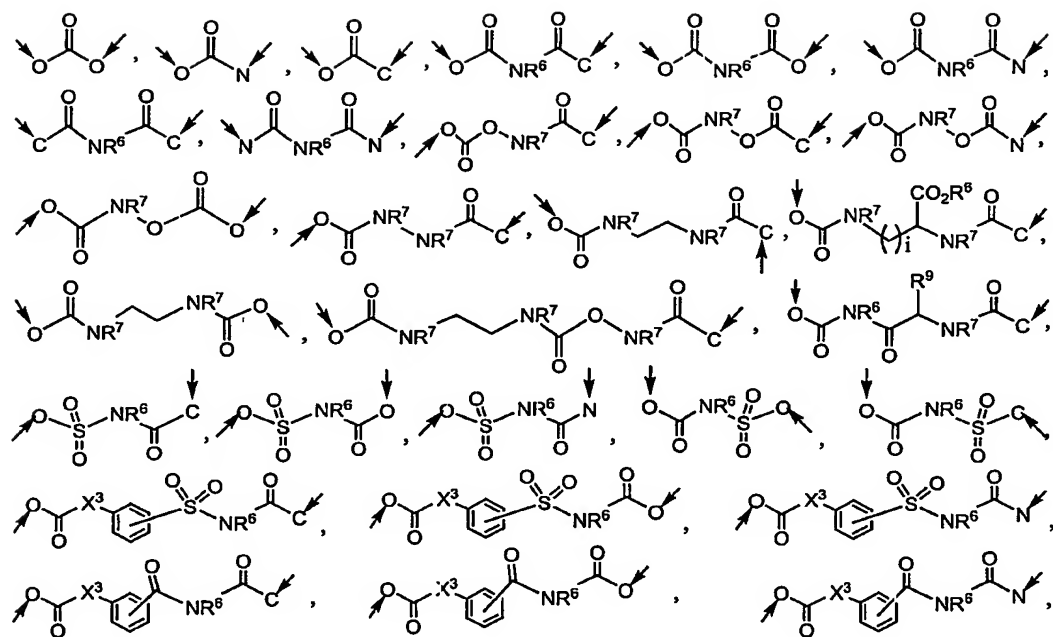
his 1-2000;

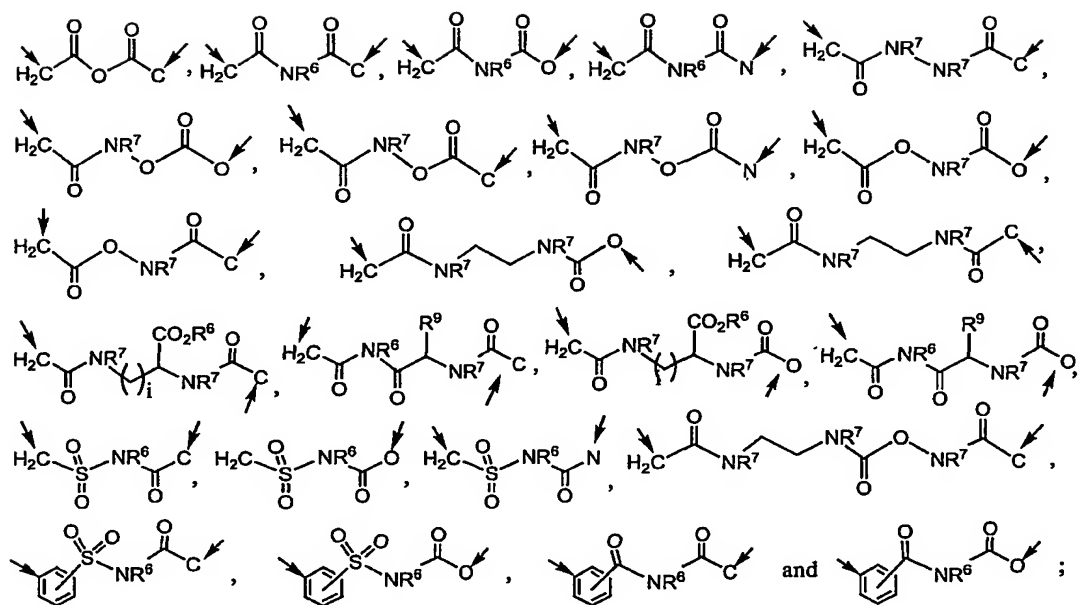
10 i is 1-4;

R^{10} and R^{11} independently represent H, (Ci- C_8)alkyl, (C_3 - C_8)cycloalkyl, or a group selected from the group consisting of:



5 R^{12} independently represents a group selected from the group consisting of:





5 and X^3 is independently O or NR^7 .

Another embodiment of the invention is a pharmaceutical composition comprising one or more compounds of formula I or intermediates thereof and one more

of pharmaceutically acceptable carriers, vehicles or diluents. Further embodiments include methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula I.

Detailed Description of the Invention

5 The present invention characterizes compositions, methods of preparation and methods of use of prodrugs, NO-releasing prodrugs, mutual prodrugs, double prodrugs, and codrugs.

 The compounds of the present invention are prodrugs or mutual prodrugs in which known therapeutic agents or potential therapeutic agents are linked covalently to
10 novel biocleavable linkers.

 The compounds of the present invention also include NO-releasing prodrugs in which a therapeutic agent is linked covalently to nitrooxy (nitrate ester) group via a novel bio-cleavable linker containing a strategically placed disulfide group at β -position to the nitrate ester. The present invention also characterizes composition of NO-releasing
15 prodrugs (i.e., nitrooxy ester or nitrate ester prodrugs), processes for their preparation, pharmaceutical composition containing them and their use.

 Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Listed below are definitions of various terms used to describe the
20 compounds of the present invention. These definitions apply to the term as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or part of a larger group.

 The term "amino-containing" refers to drug/carrier molecule with NH functional groups such as amino (both primary and secondary), amide, urea, sulfonamide, carbamate, phosphoramidate, sulfamate, hydrazone, semicarbazone, thiosemicarbazone, hydrazide, carbazate and the like. This also includes NH-containing heterocyclic
25 compounds such as imidazoles, benzimidazoles, pyrazoles, benzpyrazols, pyrrols, indoles, triazoles, tetrazoles, benzotriazoles, benzotetrazoles and their derivatives. These NH-containing heterocyclic compounds can be sub-structures of more complex
30 drug/carrier molecules. Amino group of the candidate drug can be primary or secondary (both acyclic and cyclic) which include amide-NH, sulfonamide-NH, carbamate-NH,

sulfamate-NH, hydrazide-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH, urea-NH and also drugs containing indole, imidazole, benzimidazole, thiazole, oxazole, pyrrole, pyrazole, triazole, tetrazole, or similar NH-containing heterocyclic sub-structures of a more complex drug molecule.

5 The term "hydroxyl-containing" refers to drug/carrier molecules with hydroxyl groups (primary, secondary and tertiary) including hydroxyl groups of hydroxamic acids and ketoximes derived from keto-containing molecules. Hydroxyl group of drugs can be of primary, secondary or tertiary nature.

10 The term "sulfahydryl-containing" refers to drug/carrier with free sulfahydryl (SH) group.

 The term "halo" refers to fluoro, chloro, bromo, and iodo.

 The term "halide" refers to fluoride, chloride, bromide, and iodide.

 The term "alkyl" refers to acyclic alkyl chains. For example, the term "C₁-C₈ alkyl" refers to methyl, ethyl, propyl, isopropyl, butyl, cyclobutyl, s-butyl, and t-butyl, 15 ,pentyl, hexyl, heptyl, octyl, and the like.

 The term "cycloalkyl" refers to cyclic alkyl chains, e.g., the term "C₃-C₈ cycloalkyl" refers to cyclopropyl, cyclooctyl, cyclopentyl, cyclohexyl, cycloheptyl, , cyclooctyl and the like.

 The term "aryl" refers to phenyl, naphthyl and the like.

20 The term "aralkyl" refers to benzyl, phenethyl and the like.

 The term "alkoxy" refers to both acyclic and cyclic C₁-C₈ alkyloxy. For example, the term "C₁-C₈ alkyloxy" refers to methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, butoxy, cyclobutoxy, s-butoxy, and t-butoxy, cyclopentyloxy, pentyloxy, hexyloxy, cyclohexyloxy, heptyloxy, cycloheptyloxy, octyloxy, cyclooctyloxy and the 25 like.

 The term "heterocyclic" and "heteroaryl" refers to both saturated and unsaturated 5- and 6-membered rings (including benzo-fused) containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. All of these rings may be substituted with up to three substituents independently selected from the group 30 consisting of amino, halo, alkoxy, alkyl, cyano, nitro, hydroxyl, sulfahydryl, carboxyl and the like. Saturated rings include, for example, pyrrolidinyl, piperidinyl, piperazinyl,

tetrahydrofuryl, oxazolidinyl, dioxanyl, pyranyl, and the like. Benzofused saturated rings include indolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl and the like. Unsaturated rings include furyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, tetrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, 5 thiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, and the like. Benzofused unsaturated rings include isoquinolyl, benzoxazolyl, benzthiazolyl, quinolyl, benzofuranyl, thionaphthyl, indolyl and the like.

The term "substituted alkyl" refers to acyclic and cyclic alkyl groups substituted with one or more of groups such as alkyl, aryl, hydroxy, alkoxy, cyano, carboxyl, 10 sulfahydryl, alkylthio, amino, nitro, halo, carbonyl, carbamato, sulfamato, sulfonato, sulfato, and the like.

The term "substituted aryl" refers to aryl groups substituted (including fused) with one or more of groups such as alkyl, aryl, hydroxy, alkoxy, cyano, carboxyl, sulfahydryl, alkylthio, amino, nitro, halo, carbonyl, carbamato, sulfamato, sulfonato, sulfato, and the 15 like.

The term "amino acid" refers to molecules containing one or more amino and carboxyl groups. Examples of alfa-amino acids (D-, L- and DL- amino acids) include natural alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, 20 threonine, tryptophan, tyrosine, and valine. Other examples include beta-amino acids and known unnatural amino acids.

The term "amino acid ester" as used in this specification refers to an amino acid where the carboxyl group is substituted with a C_{1-8} alkyl group. That is, the alkyl group when taken together with the carboxyl group forms a C_{1-6} alkyl ester. It is appreciated 25 that some amino acids (e.g., aspartic acid and glutamic acid) have two carboxyl groups these may form mono- and di-esters.

The term "protecting group" (PG) refers to an 'amino protecting group' or a 'hydroxyl protecting group' or a 'carboxyl protecting group' and the like.

The term "amino protecting group" refers to a group that selectively blocks or 30 protects the amino functionality in presence of other functional groups on the molecule. Examples of such amino-protecting groups include the formyl group, the trityl group, the

phthalimido group, the acetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl ("CBZ"), 9-fluorenylmethoxycarbonyl ("Fmoc"), tert-butoxycarbonyl ("BOC"), trichloroethylcarbonyl and the like. Additional examples of amino protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991. Molecules with two or more amino groups may form mono-, di-, tri-, poly-, protected derivatives depending on the reaction conditions used.

The term "hydroxyl protecting group" refers to a group that selectively blocks or protects hydroxyl functionality in presence of other reactive functional groups on the molecule. Examples of such hydroxyl-protecting groups include, for example, ether groups including methyl and substituted methyl ether groups such as methyl ether, methoxymethyl ether, methylthiomethyl ether, tert-butylthiomethyl ether, triphenylmethyl, tetrahydropuranyl (THP), (phenyldimethylsilyl)methoxy-methyl ether, benzyloxymethyl ether, p-methoxybenzyloxy-methyl ether, and tert-butoxymethyl ether; substituted ethyl ether groups such as ethoxyethyl ether, 1-(2-chloroethoxy)-ethyl ether, 2,2,2-trichloroethoxymethyl ether, and 2-(trimethylsilyl)ethyl ether; isopropyl ether groups; phenyl and substituted phenyl ether groups such as phenyl ether, p-chlorophenyl ether, p-methoxyphenyl ether, and 2,4-dinitrophenyl ether; benzyl and substituted benzyl ether groups such as benzyl ether, p-methoxybenzyl ether, o-nitrobenzyl ether, and 2,6-dichlorobenzyl ether; and alkylsilyl ether groups such as trimethyl-, triethyl- and triisopropylsilyl ethers, mixed alkylsilyl ether groups such as dimethylisopropylsilyl ether, tert-butyldimethylsilyl ether and diethylisopropylsilyl ether; and ester protecting groups such as acetate ester, formate ester, benzylformate ester, mono-, di-, and trichloroacetate esters, pivalate ester, phenoxyacetate ester, and p-chlorophenoxyacetate, benzyloxycarbonate, 9-fluorenylmethoxycarbonate, tert-butoxycarbonate, trichloroethylcarbonate, carbamate, sulfamate and the like. Additional examples of hydroxyl protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991. Molecules with two or more hydroxyl groups may form mono- and di-esters/ethers depending on the reaction condition.

The term "carboxyl protecting group" refers to a group that selectively blocks or protects carboxyl functionality in presence of other reactive functional groups on the molecule. Examples of such carboxyl-protecting groups include, for example (substituted) alkyl esters such methyl ester, ethyl ester, t-butyl ester, (substituted) benzyl ester, trichloroethyl ester, and the like. Additional examples of carboxylic acid protecting groups are described T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991. Molecules with two or more carboxylic acid groups may form mono-, di-, tri-, tetra-, poly- protected derivatives depending upon the reaction conditions used.

10 The term "carbonyl activating group" refers to leaving group ("LG") of a carboxyl derivative that is easily replaced by an incoming nucleophile. Such "LG" groups include, but are not limited to, (substituted) alkoxy, aryloxy, nitrogen containing unsaturated heterocycles such as N-oxybenzotriazole, imidazolyl, o/p-nitrophenoxy, pentachlorophenoxy, N-oxysuccinimide, N,N'-dicyclohexylisoure-O-yl, N-hydroxy-N-
15 methoxyamino, and the like; acetates, formates, sulfonates such as methanesulfonate, ethanesulfonate, benzenesulfonate, or p-toluenesulfonate, and the like; and halides especially fluoride, chloride, bromide, or iodide.

The term "carbonyl activating reagent" refers to a reagent that converts the carbonyl of a carboxylic acid group into one that is more susceptible to nucleophilic
20 attack and includes, but is not limited to, such reagents as those found in "The Peptides", Gross and Meienhofer, Eds., Academic Press (1979), Ch. 2, and M. Bodanszky, "Principles of Peptide Synthesis", 2.sup.nd Ed., Springer-Verlag Berlin Heidelberg, 1993, hereafter referred to as "The Peptides" and "Peptide Synthesis" respectively. Carbonyl group (i.e., aldehyde or keto group) of candidate drugs may be converted first to
25 aldoxime, ketoxime, hydrazone, semicarbazone and the like, before coupling to the linker. Specifically, carbonyl activating reagents include thionyl bromide, thionyl chloride, oxalyl chloride, and the like; esters of alcohols such as nitrophenol, pentachlorophenol, and the like; and compounds such as 1,1'-carbonyldiimidazole (CDI), benzotriazole, imidazole, N-hydroxysuccinimide, dicyclohexylcarbodiimide (DCC),
30 EDC, phosgene or its equivalents, N, N-dimethylaminopyridine (DMAP) and the like.

The terms "phosgene or its equivalents" refer to phosgene or its equivalents such as diphosgene, triphosgene, CDI, DSC, BTBC, alkoxycarbonyl chlorides, o/p-nitrosubstituted phenoxycarbonyl chlorides, and the like.

In general, the term "pharmaceutical" when used as an adjective means
5 substantially non-toxic to living organisms.

The terms "pharmaceutically acceptable metal ions or salts" refer to salts of the compounds of this invention, which are substantially non-toxic to living organisms. See, e.g., Berge, S. M. et al., "Pharmaceutical Salts", J. Pharm. Sci., 66:1, 1977. Typical pharmaceutical salts include those salts prepared by reaction of the compounds of this
10 invention with an inorganic or organic acid or base. Such salts are known as acid addition or base addition salts respectively. These pharmaceutical salts frequently have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions. Examples of pharmaceutically acceptable salts are those with inorganic bases such as sodium,
15 potassium, calcium, magnesium, and hydroxides, and the like, or with organic bases such as lysine, arginine, triethylamine, dibenzylamine, piperidine, and the like.

The term "suitable solvent" refers to a solvent that is inert to the ongoing reaction and sufficiently solubilizes the reactants to effect the desired reaction. Examples of suitable solvents include but are not limited to, dichloromethane, chloroform, 1,2-
20 dichloroethane, diethyl ether, tert-butylmethyl ether, acetonitrile, ethyl acetate, 1,3-dimethyl-2-imidazolidinone, tetrahydrofuran, dimethylformamide, benzene, toluene, xylene, N-dimethylacetamide, N-methylpyrrolidine, chlorobenzene, dimethylsulfoxide, dimethoxyethane, water, methanol, ethanol, isopropanol, pyridine, nitromethane, mixtures thereof, and the like.

The term "suitable base" refers to a base, which acts as a proton trap for any
25 protons, which may be produced as a byproduct of the desired reaction, or to a base, which provides a reversible deprotonation of an acidic proton from the substrate and is reactive enough to effect the desired reaction without significantly effecting any undesired reactions. Examples of such bases include, but are not limited to, carbonates,
30 bicarbonates, and hydroxides (e.g., lithium, sodium, potassium, magnesium, calcium and the like), sodium/potassium/calcium hydride, sodium/potassium alkoxide (i.e.,

methoxide, ethoxide, tert-butoxide and the like), triethylamine, diisopropylethylamine, N-methylpyrrolidine, N-methylmorpholine, tetramethylguanidine, or aromatic nitrogen containing heterocycles such pyridine, 4-(dimethylamino)pyridine (DMAP), and the like.

The term "NONOate" refers to a linkable nitric oxide-releasing group such as
5 $\text{AcOCH}_2\text{-O-N}_2\text{-N(OOR}^7, \text{OCHOCH}_2\text{-O-N}_2\text{-N(O}^-\text{) R}^7\text{R}^7, \text{CH}_2\text{-O-N}_2\text{-N(OOR}^7 \text{ R}^7$ and the like.

The term "therapeutic agent" refers to biologically active molecules such as drugs, vitamins, and other molecules, agents or substances concerned with or contributing to the treatment and cure of illness or contributing to the general well being of a mammal or
10 human. The therapeutic agents can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity®, Prous Science Drugs of the Future™, The Ensemble® and the like. The Merck Index is a one-volume encyclopedia of chemicals, drugs and biologicals that contains more than 10,000 monographs. Each monograph in this authoritative reference source is a concise
15 description of a single substance or a small group of closely related compounds. Prous Science is an international health science publishing company, established in 1958 and headquartered in Barcelona, Spain. Prous Science Drugs of the Future™, produced by Prous Science Publishers, contains comprehensive drug monographs providing product information on new compounds, including the synthesis and corresponding schemes,
20 pharmacological action, pharmacokinetics and metabolism, toxicity, clinical studies, manufacturer, and references. Information on compounds is continuously updated as advances in development status are disclosed worldwide. The Prous Science Integrity™ is a drug R&D portal where knowledge areas are coordinated to provide a harmonious and interrelated whole, which includes Drugs & Biologies, Targets, Organic Synthesis,
25 Experimental Pharmacology, Pharmacokinetics and Metabolism, Clinical Studies, Disease Briefings, Companies & Markets, Literature and Patents. The *Investigational Drugs database (IDdb)*, developed by Thomson Current Drugs, is a pharmaceutical competitor intelligence service. It covers all aspects of investigational drug development, from first patent to eventual launch or discontinuation. The Ensemble® on the Web
30 provides essential information, including chemical structures, on more than 140,000

compounds with demonstrated biological activity in the drug research and development pipeline.

The term "vitamin" includes vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5.

The term "peptide" includes large and small peptides, including, but not limited to, targetable small peptides such as a dipeptide, tripeptide, tetrapeptide, etc.

The term "ligand" means a small molecule that binds to a larger macromolecule, whether or not the ligand actually binds at a metal site. Such ligands can be small peptides.

One aspect of the invention is to provide mutual prodrugs of two or three therapeutic agents currently used for use in combination therapy utilizing novel bio-cleavable linkers, water-soluble prodrugs of insoluble and sparingly-soluble therapeutic agents using the same linker technology, and water-soluble double and triple prodrugs of sparingly-soluble therapeutic agents using the same linker technology. The embodiments of the invention may also comprise vitamins and targetable small peptides in addition to or in place of a promoeity to yield targetable prodrugs.

The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or from different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with similar mechanism of action or act on different biological targets with different mechanisms of action.

To be considered for prodrug synthesis, the candidate drugs should contain one or more of the essential functional groups such as amino, hydroxyl, keto, or carboxyl groups in their structure.

Amino group of the candidate drug can be primary or secondary (both acyclic and cyclic) which include amide-NH, sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH and also drugs containing indole, imidazole, benzimidazole, thiazole, oxazole, pyrrole, pyrazole, triazole, tetrazole, or similar NH-containing heterocyclic sub-structures of a more complex drug molecule. Similarly, hydroxyl group of drugs can be of primary, secondary or tertiary nature. Keto

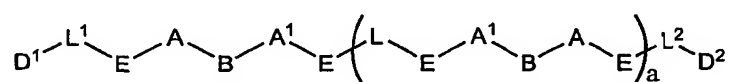
group of candidate drugs may be converted first to ketoxime, hydrazone, semicarbazone and then like, before coupling to the linker. Obviously, hydroxyl or amino functions thus generated will be used to form covalent bond between the drug and the linker.

5 The candidates for making mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (including those combination studies at investigational stage) in various therapeutic areas provided each of those drugs possesses the requisite functional group(s). There are a number of therapeutic areas where such combination therapy is applied routinely and successfully.

10 On the basis of the proposed sulfahydryl-dependent mechanism of NO-release from GTN, we have designed the compounds and prodrugs of the present invention where a suitable drug molecule is linked covalently to a nitrooxy (nitrate ester) group via a bio-labile linker containing strategically located disulfide bond at Z?efø-position to nitrate ester. In vivo, the disulfide bond in the prodrug is expected to be reduced by endogenous sulfahydryl-containing species such as glutathione (GSH) to generate a
15 reactive thiolate anion (i.e., *beto*-mercapto-nitrate), which can trigger further break-down of the linker moiety to release the free drug (via a mechanism as shown Scheme M1) and NO simultaneously at the same location. It is possible, as depicted in the mechanism Scheme M1, the release of NO can go via a hypothetical cyclic transient intermediate 'b'. Similar hypothetical mechanism was proposed for NO release from SS-nitrates, which,
20 were also designed on the basis of a sulfahydryl-dependent NO release from GTN. See, for example, Zavorin, S. I. et al., Organic Letters, 2001, 3, 1113, incorporated herein in its entirety. Mutual prodrugs can be made by linking covalently any two of the following: an amino-containing therapeutic agent to another ammo-containing therapeutic agent; an amino-containing therapeutic agent to a hydroxyl-containing therapeutic agent; an amino-
25 containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; a hydroxyl-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; an amino-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; an amino-containing therapeutic agent to a keto-containing therapeutic agent or its hydrazone, semicarbazone or oxime derivative and the likes; a
30 hydroxyl-containing therapeutic agent to a keto-containing therapeutic agent via its hydrazone, semicarbazone, or oxime derivative and the likes.

Another aspect of the present invention is to provide new nitrate ester (NO-releasing) prodrugs of many types of existing drugs using novel biocleavable linkers. Such prodrugs are expected to exhibit better efficacy and tolerability with reduced side effects compared to the corresponding original drugs.

- 5 An embodiment of present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof:



Formula (I)

- 10 wherein,

a is 0-2;

B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_c$, S-S, S-S=O, S-SO₂ or S-S=NH;
b is 1-6; c is 1-1000;

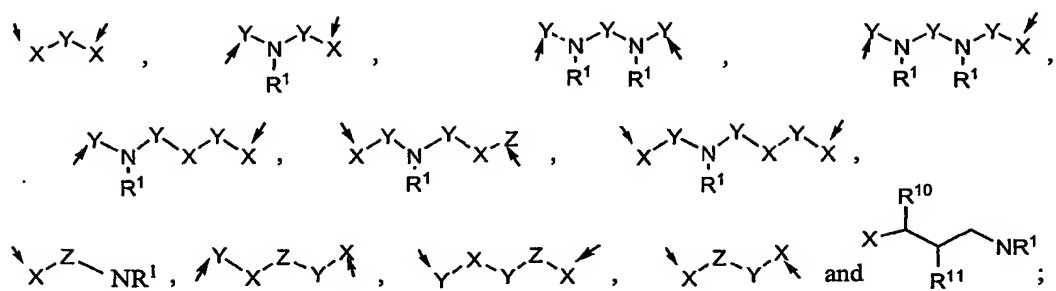
- 15 A and A¹ independently represent a bond, $(CH_2)_d$, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;
d is 1-8;

D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OC(=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹)C(=O)NHR¹ and -N(R¹)SO₂NHR¹;

- 20 D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, NO₂, a linkable nitric oxide-releasing group comprising a NONOate, a group comprising one or more of water-solubilizing functional groups, or a polymer;

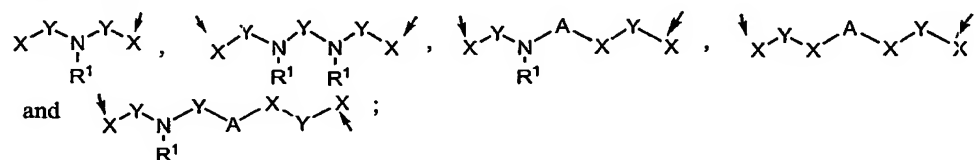
E independently represents CH₂ or a bond;

- 25 L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:



L is R^{12} or a group with bonding in any direction, independently selected from the group consisting of:

5



X independently represents a bond, C, O, S, or NR^1 ;

Y independently represents a bond, $\text{C}=\text{O}$, $\text{C}=\text{S}$, $\text{S}=\text{O}$, SO_2 , $\text{P}(=\text{O})\text{XR}^1$ or $(\text{CH}_2)_d$;

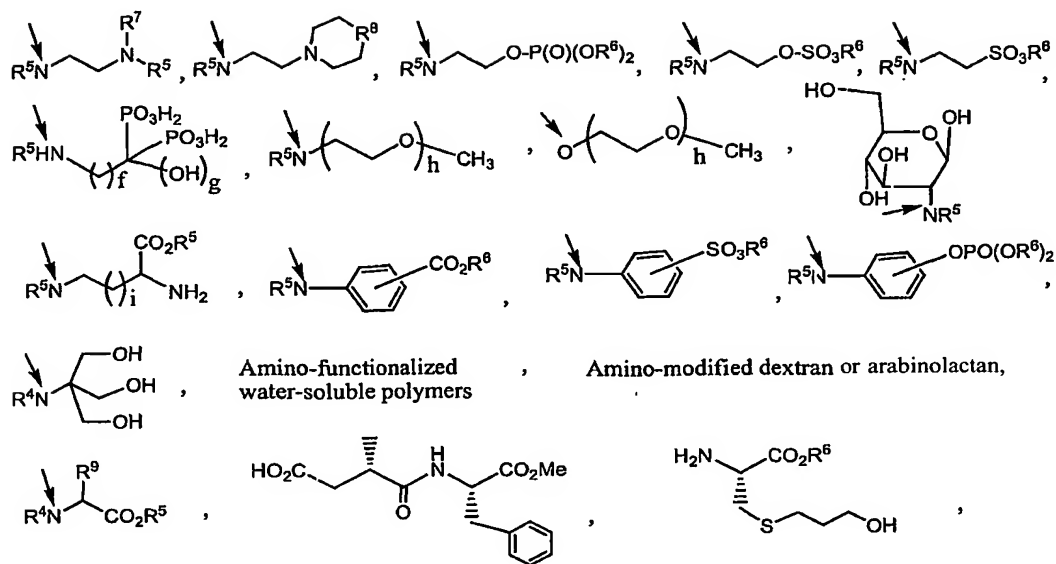
Z independently represents a bond, or $(\text{CH}_2)_j$; wherein, j is 1-4;

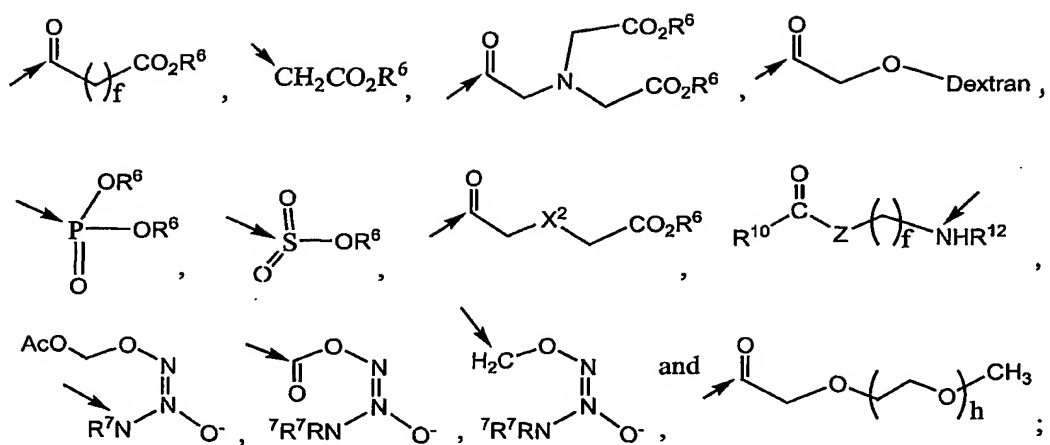
10 R^1 independently represents a bond, H, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_5-\text{C}_{14})\text{aryl}$, aralkyl or M^{6+} ;

R^2 independently represents H, NH_2 , or NHAc ;

R^3 independently represents H, CO_2R^5 , $\text{CH}_2\text{CO}_2\text{R}^5$,

R^4 independently represents H, OH, $\text{O}-(\text{C}_1-\text{C}_8)\text{alkyl}$, OM^{e+} , or a group selected from the group consisting of:

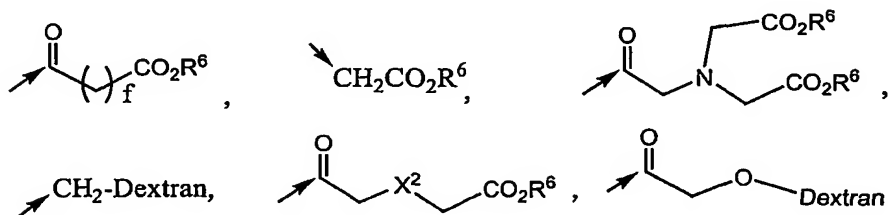




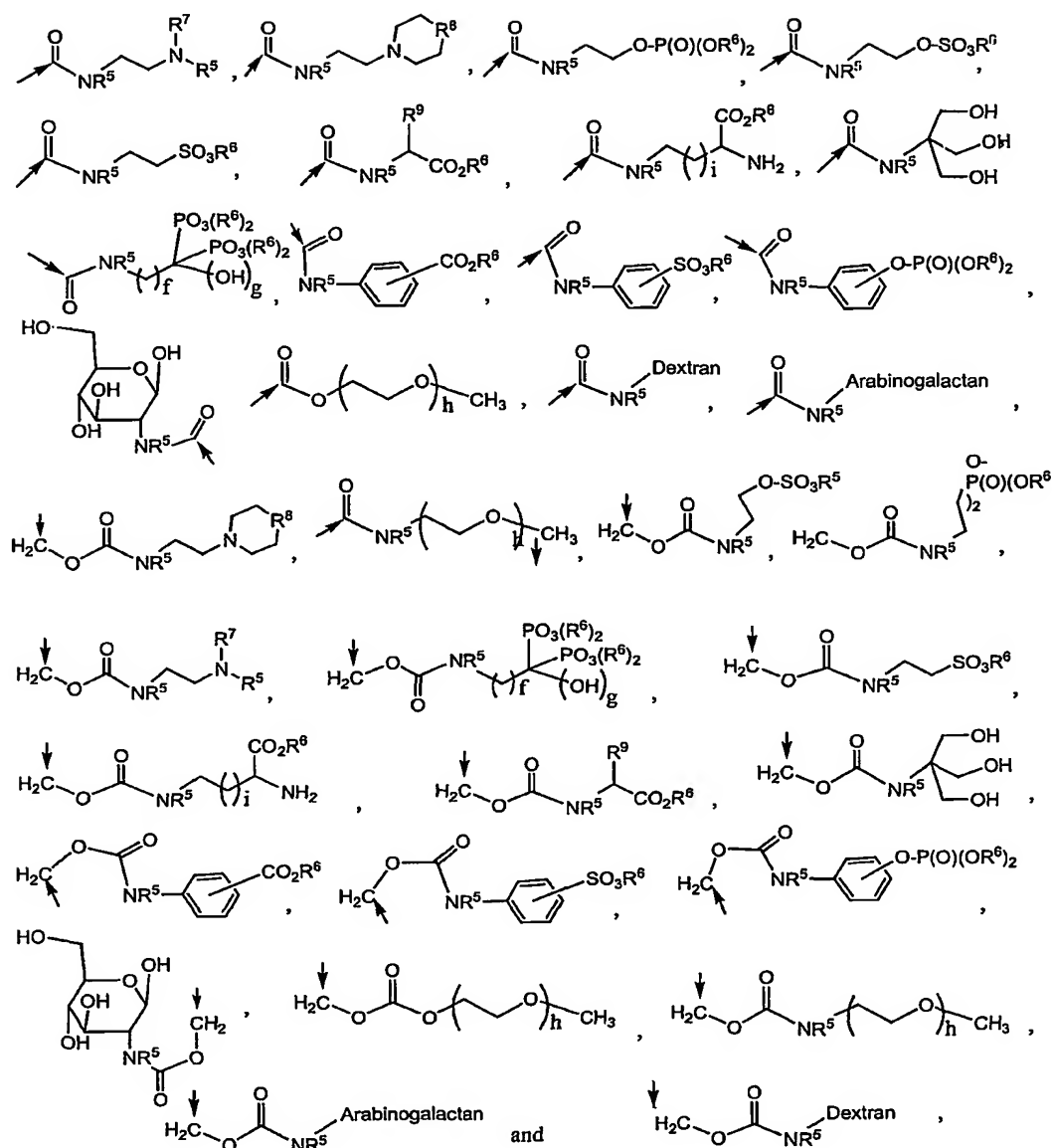
M independently represents Na, K or a pharmaceutically acceptable metal ion,

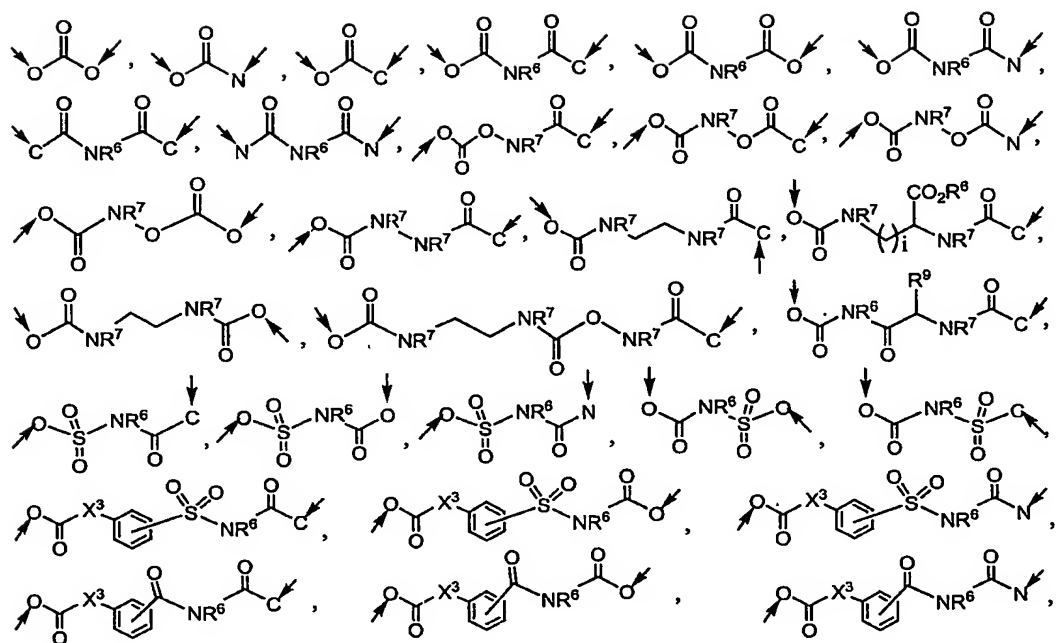
5 e = 1-3,

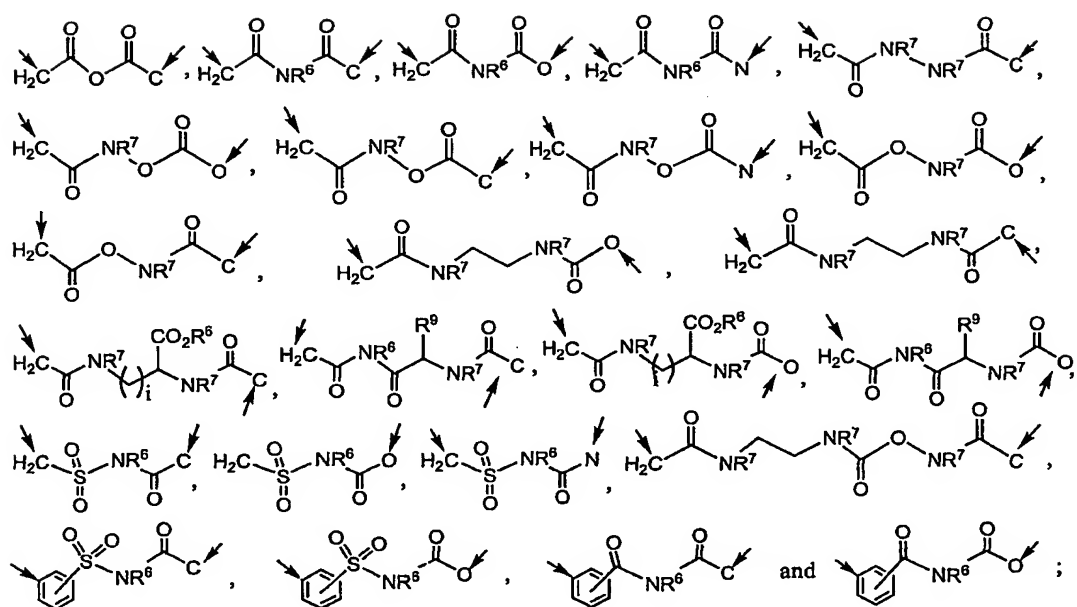
R^5 independently represents at each occurrence H, M^{6+} , (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, substituted (C_5-C_{14}) aryl, hetero (C_2-C_{14}) aryl, $C(=O)(CH_2)_fCHR^9CO_2R^5$, $CH_2C(=O)OR^5$, $P(=O)(OR^5)_2$,



- X^2 independently represents O, S, SO, SO_2 , or NR^5 ;
 R^6 independently represents H, Na^+ , K^+ , any other pharmaceutically acceptable metal ion, (Ci- C_8)alkyl, or (C_3 - C_8)cycloalkyl,
 R^7 independently represents at each occurrence same or different R^5 ;
- 5 R^8 independently represents CH_2 , O, NR^4 , S, S=O or O=S=O;
 R^9 independently represents H, (Ci- C_8)alkyl or an amino acid;
f is 0-6;
g is 0-1;
h is 1-2000;
- 10 i is 1-4;
 R^{10} and R^{11} independently represent H, (Ci- C_8)alkyl, (C_3 - C_8)cycloalkyl, or a group selected from the group consisting of:







5 X^3 is independently O or NR^7 .

D^1 and D^2 of the present invention can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity[®],

Prous Science Drugs of the Future™, The Ensemble® and the like. In a double prodrug, D¹ and D² are the same drugs. In a mutual prodrug, D¹ and D² are different drugs. In some prodrugs, only D¹ is a drug and D² may not be a drug at all. The -OH, -SH, -NH₂, -NHR¹, -CO₂H, -CONHR¹, -OCC(=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹CC=O)NHR¹ and -N(R¹SO₂NHR¹) functional groups in D¹ and D² of formula I participate in the formation of linkages between the drug and the linker. Accordingly, some of the atoms or groups in L¹ and L² may come from the corresponding D¹, D² or linker.

Another embodiment of the invention is the compound of formula I, wherein D² is an amino-, carboxyl- or hydroxyl- containing group or molecule comprising one or more water solubilizing functional groups selected from the group consisting of hydroxyl, amino, acylamino, carboxyl, sulphate, sulfonate, phosphate, phosphonate, N-acylsulfonamide, N-acylsulfamate, N-acylcarbamate, N-acylcarbamate metallic salts, and amino acids to give water-soluble prodrug.

Another embodiment of the invention is the compound of formula I, wherein D² is selected from the group of D, L and DL amino acids consisting of Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.

Another embodiment of the invention is the compound of formula I, wherein D² represents a polymer selected from the group consisting of arabinogalactan, polyamino acids, polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyacrylic acid, poly(2-hydroxyethyl 1-glutamine), dextran and modified dextrans such as dextran aldehyde, carboxymethyl dextran, arabinogalactane aldehyde, carboxymethyl arabinogalactane, and hyaluronic acid.

Yet another embodiment of the invention is the compound of formula I, wherein D² is a polyaminoacid selected from group consisting of poly(l-glutamic acid), poly(d-glutamic acid), poly(dl-glutamic acid), poly(l-aspartic acid), poly(d-aspartic acid), poly(dl-aspartic acid), copolymers of the polyaminoacids and polyethylene glycol,

Another embodiment of the invention is the compound of formula I, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltons. Yet another

embodiment of the invention is the compound of formula I, wherein the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.

In a further embodiment D² is a peptide, protein or monoclonal antibody for achieving targeted delivery of prodrugs and drugs. Another embodiment of the invention is the compound of formula I, wherein D² is a ligand or dipeptide or a dipeptide ligand. In a further embodiment D² is a dipeptide ligand that is a substrate for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. In a further embodiment D² is a targetable small peptide, i.e., dipeptide, tripeptide, tetrapeptide, etc.

Another embodiment of the invention is the compound of formula I, wherein D² is a vitamin. Such vitamin-conjugated prodrugs are expected to be taken up by the diseased cells via receptor-mediated endocytosis. In a further embodiment of the invention is a compound of formula I, wherein D² is selected from the group of vitamins consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D₂, vitamin D₃, vitamin D₄, vitamin E, menadoxime, menadiol, and vitamin K₅.

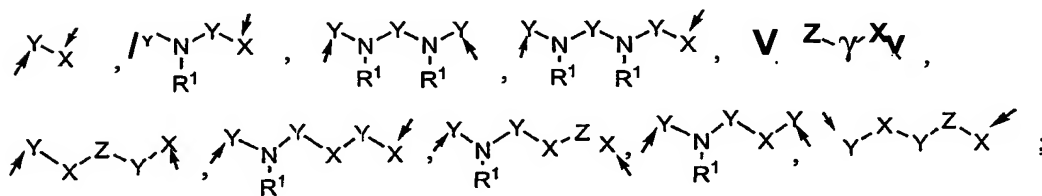
Another embodiment of the invention is the compound of formula I, wherein D¹ and D² represent the same therapeutic agent to give a symmetrical double prodrug. Another embodiment of the invention is the compound of formula I, wherein D¹ and D² represent different therapeutic agents to give a mutual prodrug. Another embodiment of the invention is the compound of formula (I), wherein D¹ and D² can be either from same or different therapeutic class. Another embodiment of the invention is the compound of formula (I), wherein D¹ and D² can be same or different therapeutic agents. Such therapeutic agents may have same or different mechanisms of action or they may work on different biological targets or work on different disease conditions.

Another embodiment of the invention is the compound of formula I, wherein D² is R², R³ or R⁴. Another embodiment of the invention is the compound of formula I, wherein a is 0, B is S-S, S-S=O, S-SO₂ or S-S=NH. Yet another embodiment of the invention is the compound of formula I, wherein a is 0, B is S-S or S-S=O, S-SO₂ and D² is R² or R³ or R⁴. A further embodiment of the invention is the compound of formula I, wherein B is S-S, A and A¹ are CH₂-CH₂, E is a bond and D² is R², R³ or R⁴.

Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; A and A¹ are CH₂-CH, E is a bond and D² is R⁴. Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S; A and A¹ are CH₂-CH₂, E is a bond and D² is R⁴.

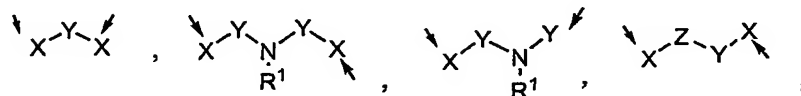
- 5 Another embodiment of the invention is the compound of formula I, wherein a is 0, B is a bond, (CH₂)_b, or (CH₂CH₂O)₀; wherein b and c are as defined above. Another embodiment of the invention is the compound of formula I, wherein a is 0, B is a bond, (CH₂)_b or (CH₂CH₂O)₀ and D² is R² or R³ or R⁴; wherein b and c are as defined above.

- Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; D¹ and D² are drug molecule or R² or R⁴ containing carboxyl group; L¹ and L² are independently selected from the following linkages:



- wherein, X, R¹, Z are as defined above; and Y is C=O. In another embodiment, A and A¹ are CH₂-CH₂, and E is a bond. In a further embodiment, A and A¹ are 1, 2-phenylene, 1, 3-phenylene or 1, 4-phenylene, and E is CH₂.

- Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S=O, S-SO₂; D¹ and D² are drug molecule or R² or R⁴ containing amino- or hydroxyl group; L¹ and L² are independently selected from the following linkages:

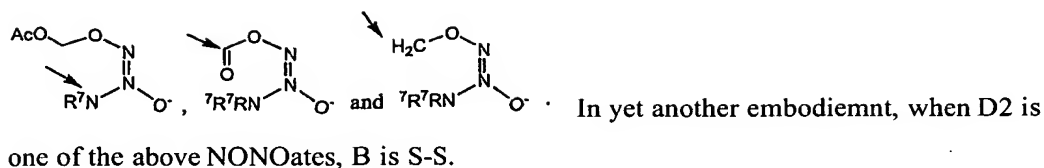


wherein, X, R¹, Z are as defined; and Y is C=O. In another embodiment, A and A¹ are CH₂-CH₂, and E is a bond. In a further embodiment, A and A¹ are 1, 2-phenylene, 1, 3-phenylene or 1, 4-phenylene, and E is CH₂.

5 Yet another embodiment of the invention is the compound of formula I, wherein a is O, B is S-S or S-S=O, S-SO₂ and D² is D¹. Another embodiment of the invention is the compound of formula I, wherein a is O; B is S-S or S-S=O, S-SO₂; A and A¹ are CH₂-CH₂, E is a bond and D² is D¹. Another embodiment of the invention is the compound of formula I, wherein a is O; B is S-S or S-S=O, S-SO₂; A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and D² is D¹ or R² or R³ or R⁴. Another
10 embodiment of the invention is the compound of formula I, wherein a is O; B is S-S; A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and D² is D¹ or R² or R³ or R⁴. A further embodiment of the invention is the compound of formula I, wherein B is S-S, A and A¹ are CH₂-CH₂, E is a bond and D² is D¹.

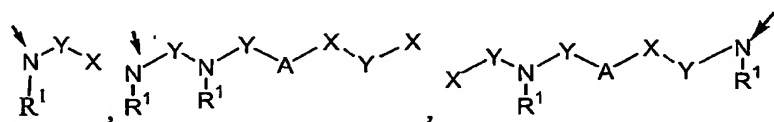
15 Yet another embodiment of the invention is the compound of formula I, wherein a is O; B is S-S or S-S=O, S-SO₂; A and A¹ are CH₂-CH₂, E is a bond and D² is a dipeptide ligand. Yet another embodiment of the invention is the compound of formula I, wherein a is O; B is S-S; A and A¹ are CH₂-CH₂, E is a bond and D² is a dipeptide ligand. The peptide ligands used in the invention can be substrates for intestinal transporters for
20 selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. An embodiment of the present invention is the compounds of formula (I), wherein D¹, L¹ and L² are as defined above; A and A¹ are CH₂; E is CH₂; B is a bond or (CH₂)_b; b is 1-6; a is O; and D² is D¹ or R² or R⁴.

Another embodiment of the present invention is the compound of formula (I),
25 wherein E, D¹ and L¹ are as defined; L² is O; A and A¹ are independently (CH₂)_d, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; d is 1-4; B is S-S, S-S=O, S-SO₂ or S-S=NH; a is O; D² is NO, NO₂ or a nitric oxide releasing molecule such as NONOate. In a further embodiment, D² is a NONOate selected from the group consisting of:



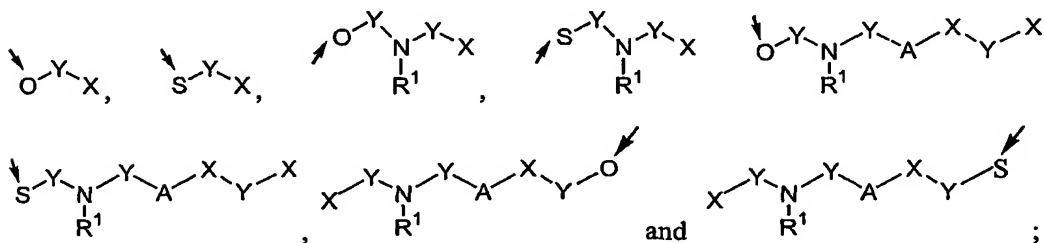
Another embodiment of the present invention is the compound of formula (I), L² is O; A and A¹ are independently (CH₂)_a, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; d is 1-4; B is S-S; a is 0; D² is NO₂. In a further embodiment, when A and A¹ are CH₂-CH₂, E is a bond. In yet another embodiment, when E is CH₂, A and A¹ are independently 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene.

Yet another embodiment of the present invention is the compound of formula (I), wherein D¹ is a amino containing drug molecule having the following reactive functional groups which are involved in the formation of L¹ linkages between the drug and the linker: -NH₂, -NHR¹, -CONHR¹, -O-C(K)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -NR¹Q=O)NHR¹ or -N(R¹SO₂NHR¹; L² is O; E is bond; L¹ is linkages selected from the group consisting of:



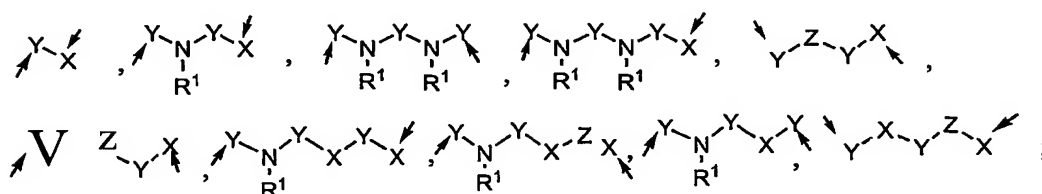
wherein, X is independently a bond, O or NR¹, Y is C=O or SO₂, A and A¹ are CH₂CH₂, B is S-S, a is 0 and D² is NO₂.

An embodiment of the present invention is the compound of formula (I), wherein D¹ is a hydroxyl or sulfahydryl containing drug molecule such as Drug-OH or Drug-SH, wherein functional groups OH and SH are involved in the formation of L¹ linkages between the drug and the linker; L² is O; E is bond, L¹ is a linkage selected from the group consisting of:



wherein, X is independently a bond, O or NR^1 , R^1 is not a bond, Y is $\text{C}=\text{O}$ or SO_2 , A and A^1 are CH_2CH_2 ; B is S-S; a is 0; and D^2 is NO_2 .

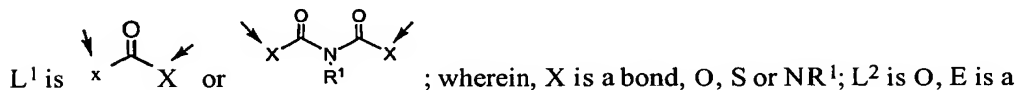
- An embodiment of the present invention is the compound of formula (I), wherein D^1 is a drug molecule having carboxyl ($-\text{CO}_2\text{H}$) as a reactive functional group such as -
- 5 CO_2H which is involved in the formation of L^1 linkages between the drug and the linker; L^2 is O; E is bond; L^1 is O or NR^1 or a linkage selected from the group consisting of:



- wherein, X is independently a bond, O or NR^1 , R^1 is not a bond; Y is $\text{C}=\text{O}$ or SO_2 ; A and
- 10 A^1 are CH_2CH_2 ; B is S-S; a is 0 and D^2 is NO_2 .

- Another embodiment of the present invention is the compounds of formula (I), wherein D^1 is an antioxidant or free radical scavenger such as a hydroxyl-containing stable radical such as a 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (4-hydroxy-TEMPO), 4-carboxy-2,2,6,6-tetramethylpiperidin-1-oxyl (4-carboxy-TEMPO) or any
- 15 other amino-/carboxyl-/hydroxyl-containing antioxidants or radical/super oxide scavengers, and D^2 is NO_2 . The amino-/carboxyl-/hydroxyl-containing antioxidants and radical/super-oxide scavengers can be known or investigational.

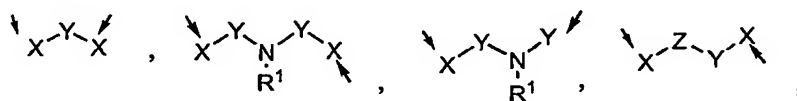
An embodiment of the present invention is the compound of formula (I), wherein



- 20 bond; A and A^1 are CH_2CH_2 ; B is S-S; a is 0; and D^2 is NO_2 .

An embodiment of the present invention is the compounds of formula (I), wherein D^1 and L^1 are as defined above; L^2 is O; A is 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; A^1 is CH_2 ; E is CH_2 ; B is S-S; a is 0 and D^2 is NO_2 .

- 5 An embodiment of the present invention is the compounds of formula (I), wherein L^2 is O; A and A^1 are CH_2 ; E is CH_2 ; B is a bond or $(CH_2)_b$; b is 1-6; a is 0; D^2 is NO_2 and L^1 is a group selected from

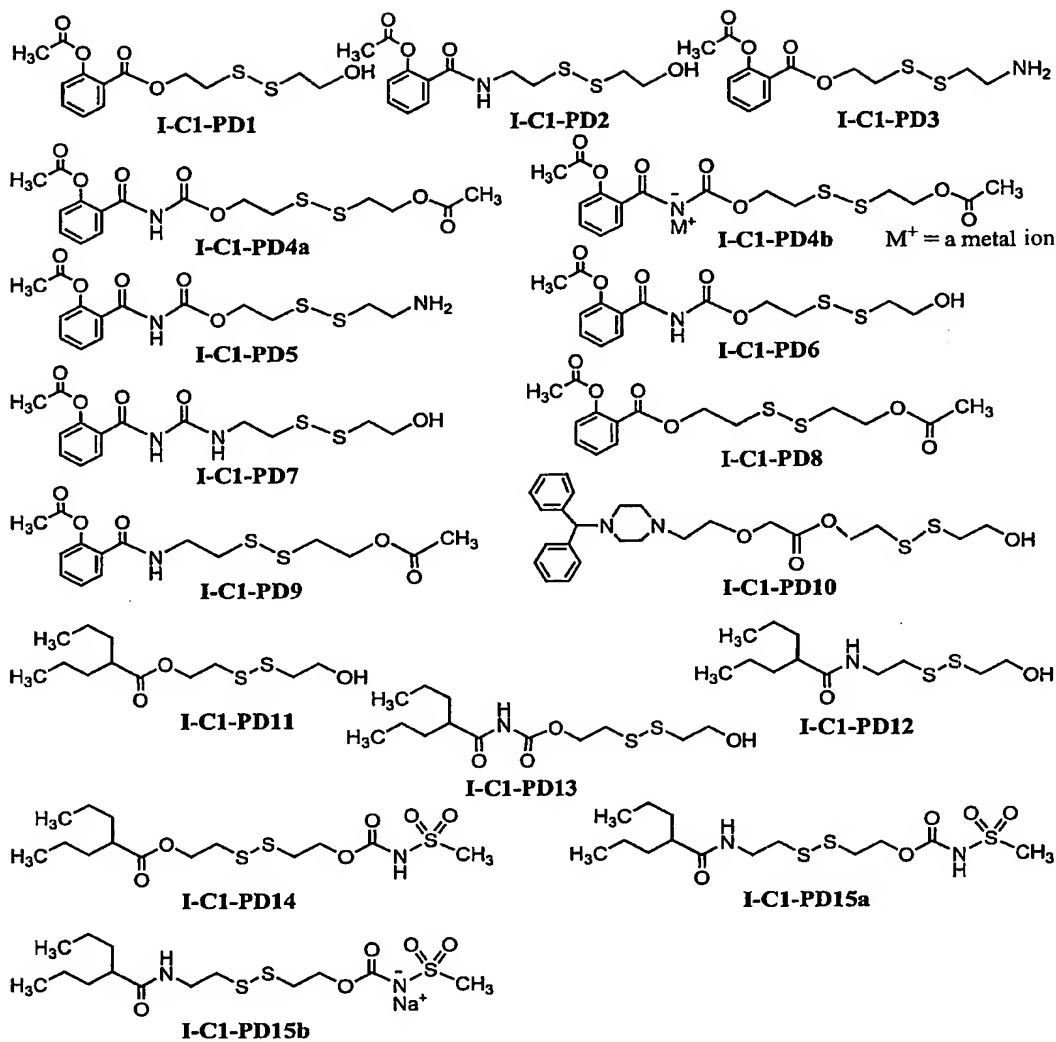


wherein, X is O, S or NR^1 ; R^1 is as defined.

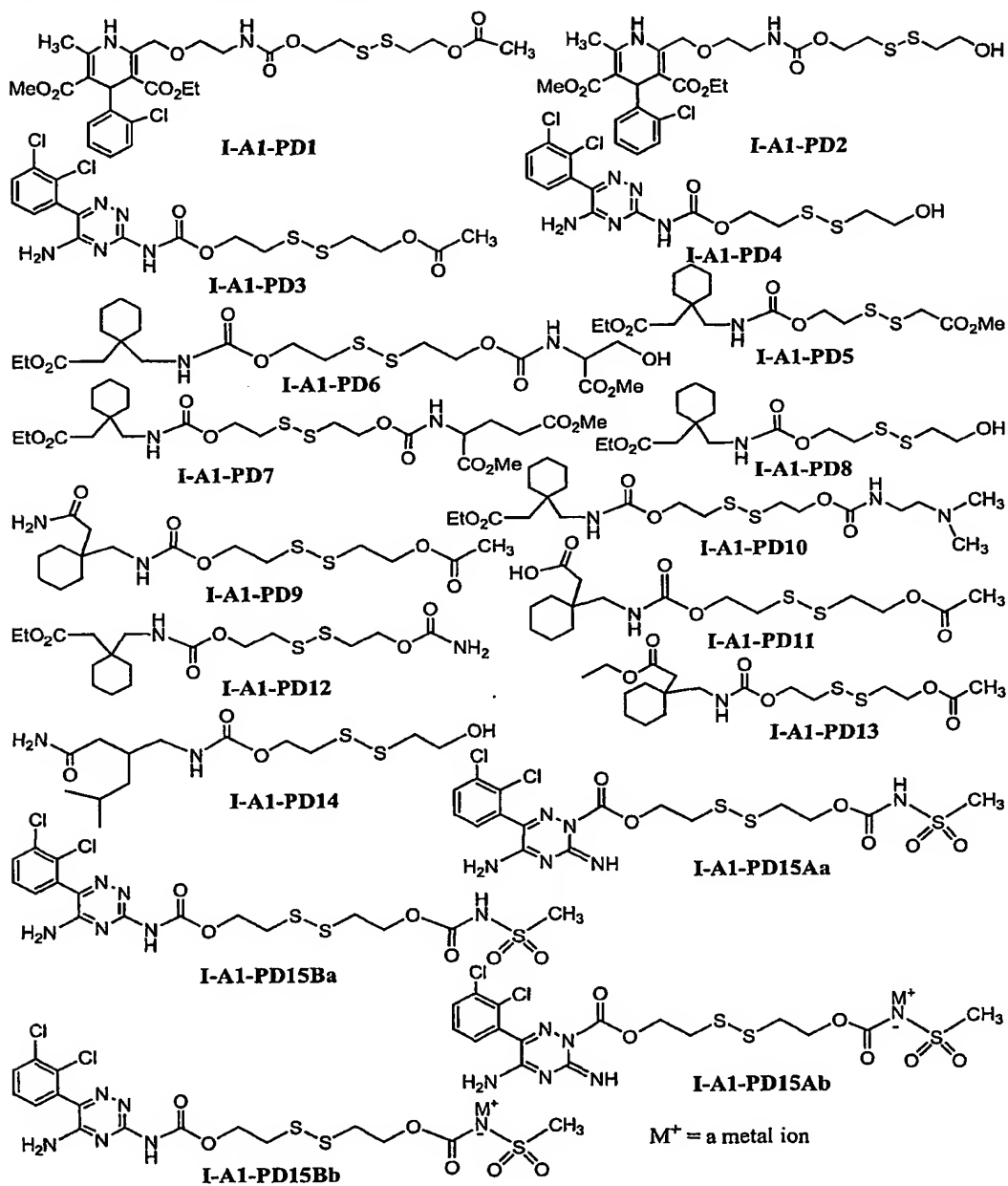
- 10 An embodiment of the invention is the compound of formula I selected from the groups consisting of:

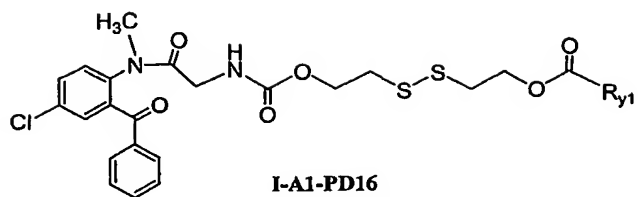
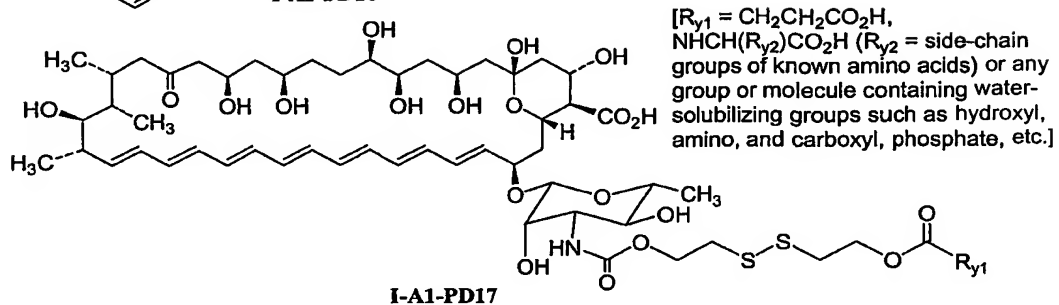
A. Prodrugs:

(a) From carboxyl-containing drugs:

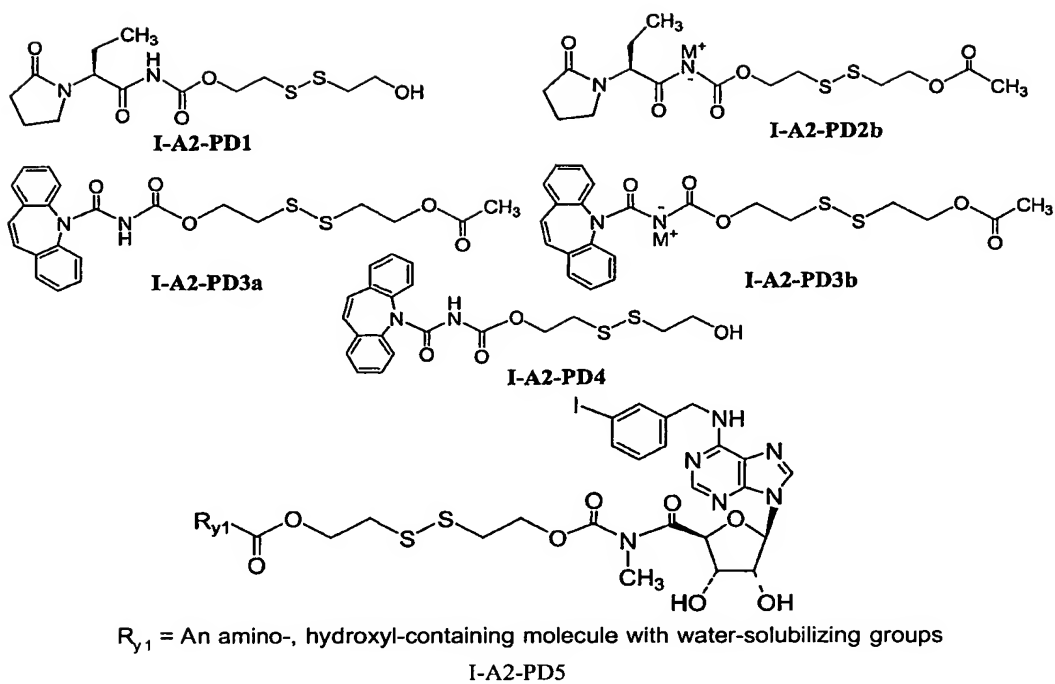


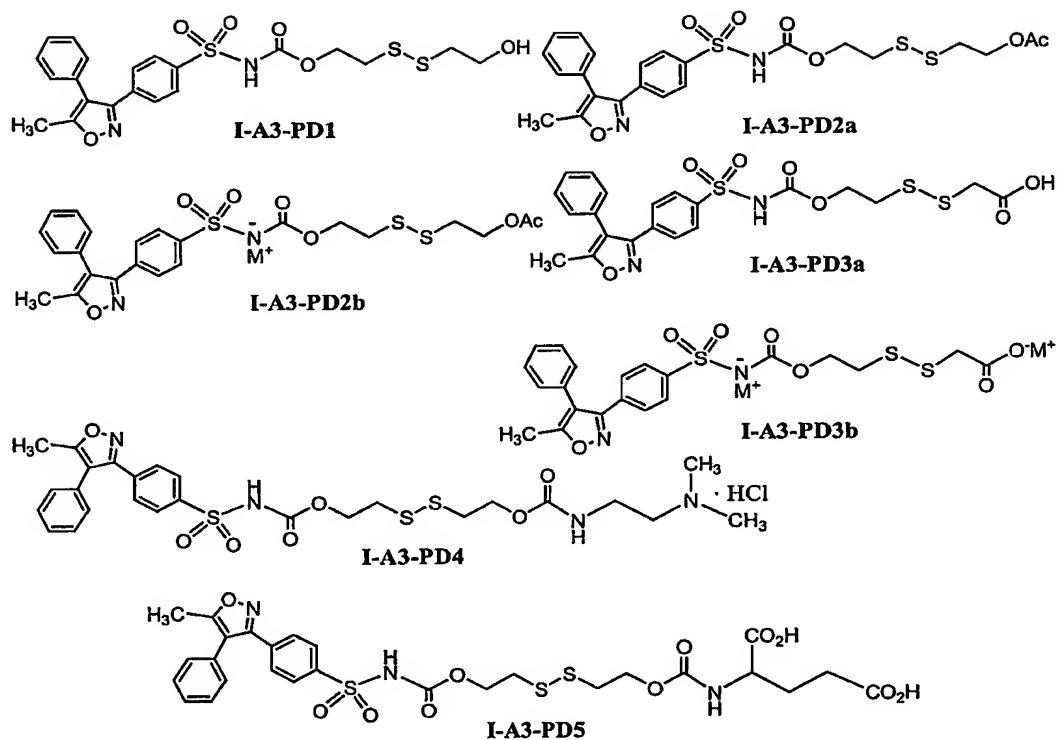
(b) From amino-containing drugs:

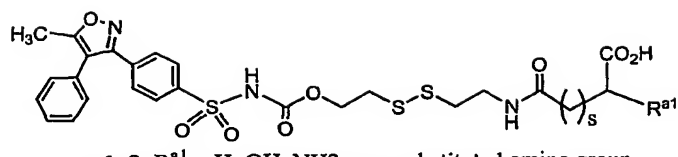
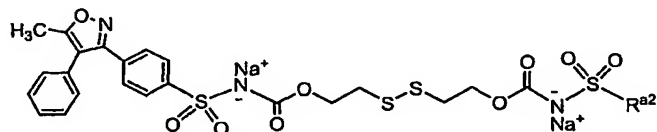


**I-A1-PD16****I-A1-PD17**

[R_{y1} = CH₂CH₂CO₂H,
NHCH(R_{y2})CO₂H (R_{y2} = side-chain
groups of known amino acids) or any
group or molecule containing water-
solubilizing groups such as hydroxyl,
amino, and carboxyl, phosphate, etc.]





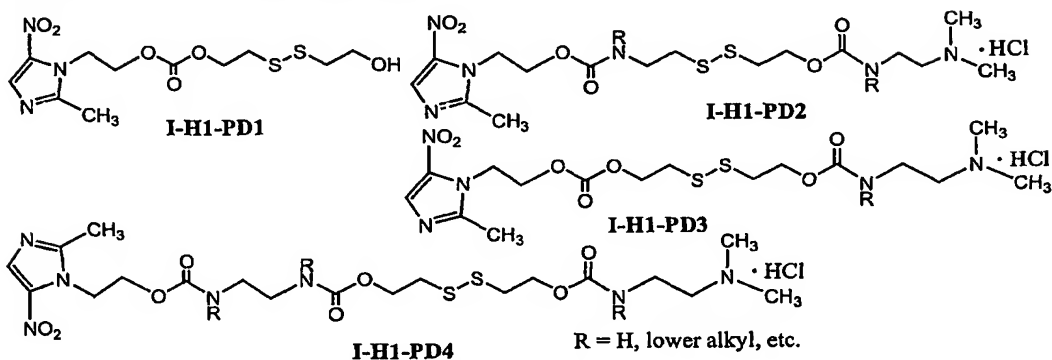
**I-A3-PD6**

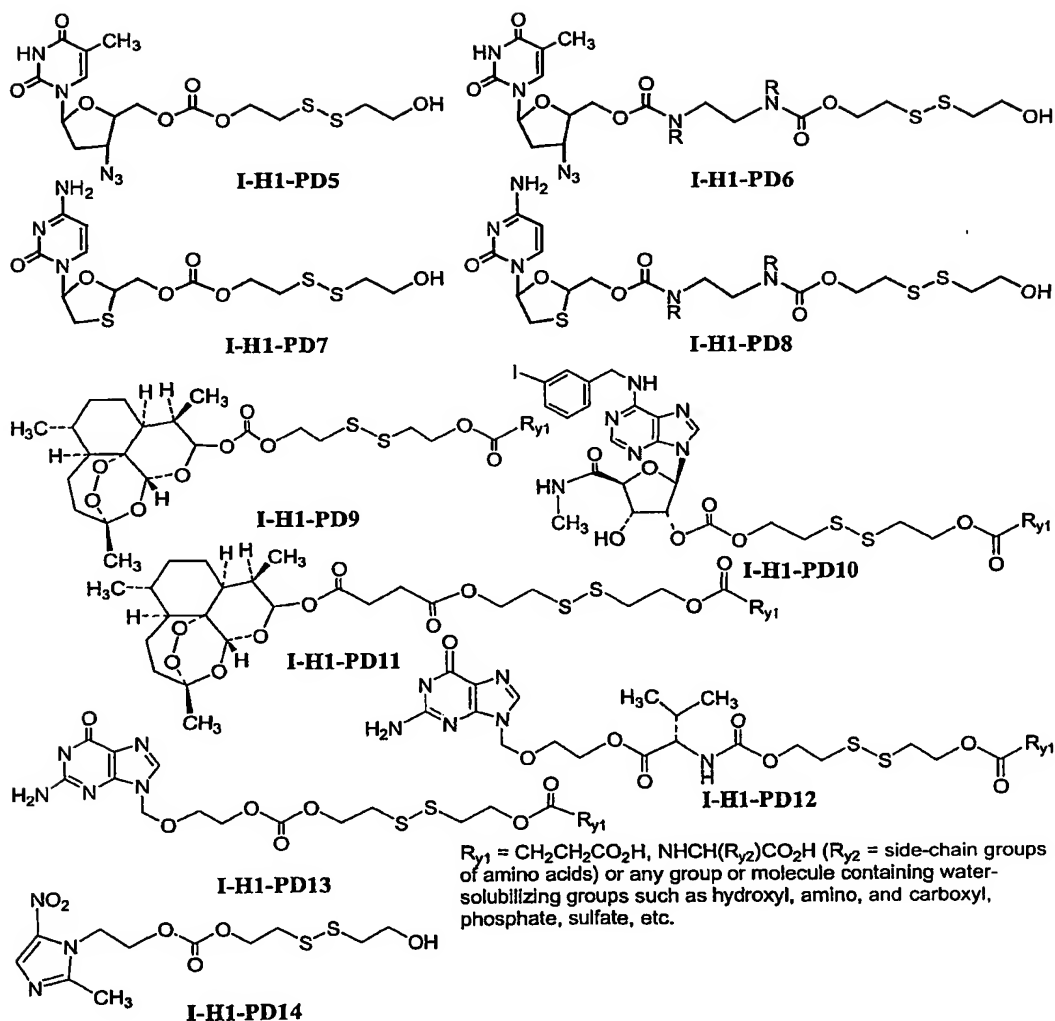
$R^{a2} = \text{Me or any alkyl, aryl, aralkyl, or another sulfonamide containing drug such as valdecoxib, celecoxib, and the like.}$

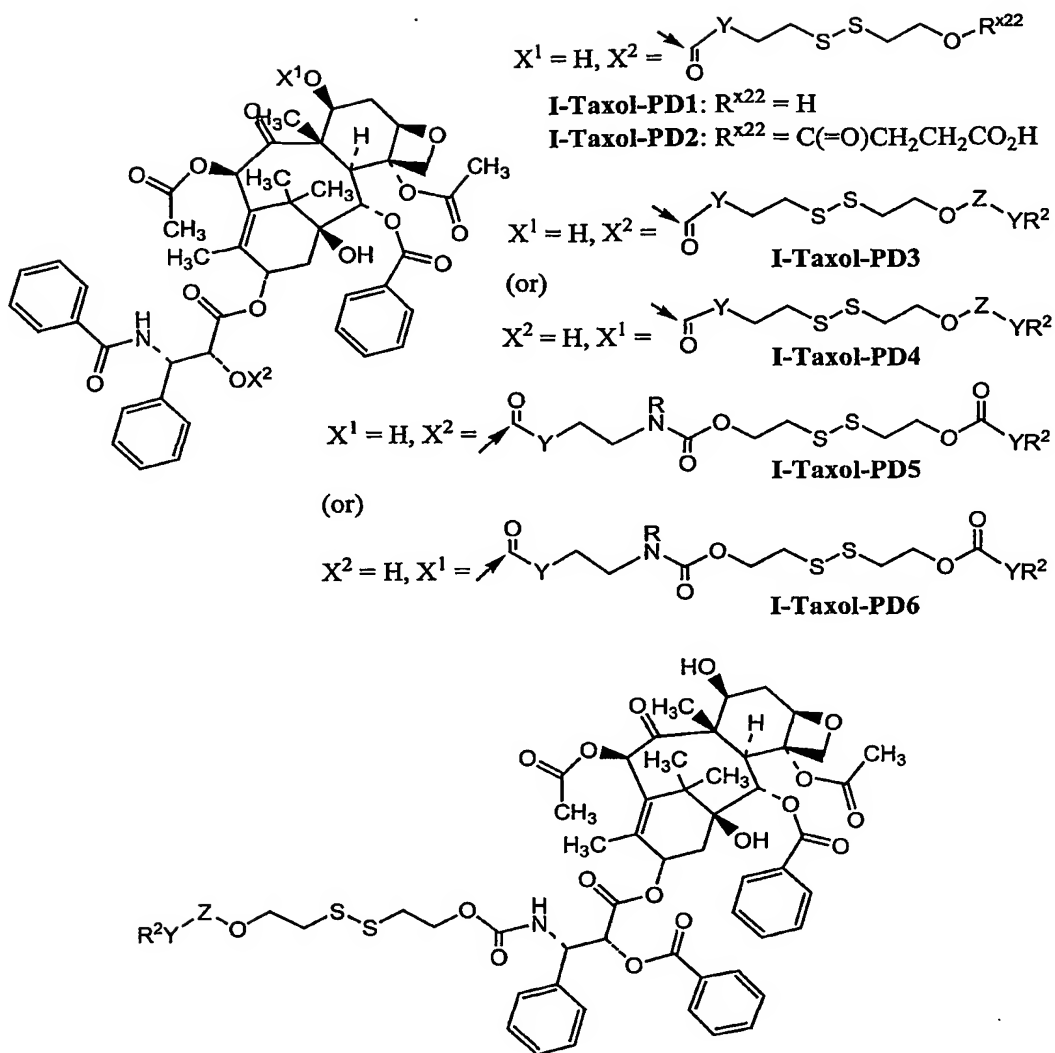
I-A3-PD7b

5

(c) From hydroxyl-containing drugs:







A PRODRUG OF ISOTAXEL

I-S23-PD1

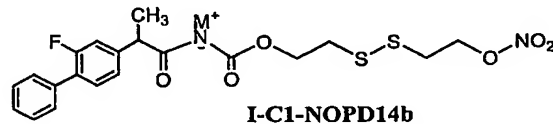
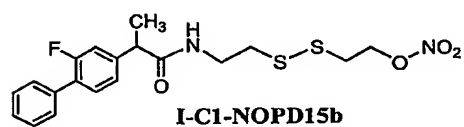
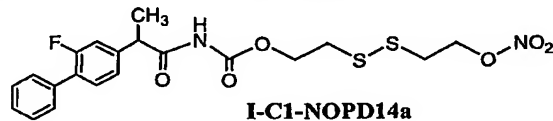
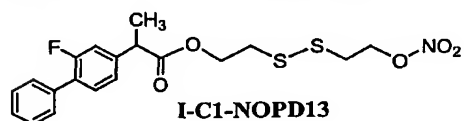
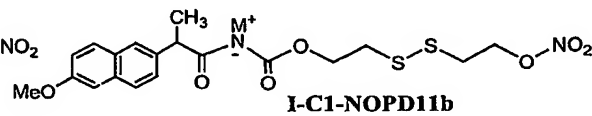
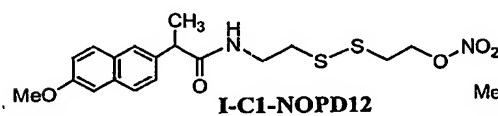
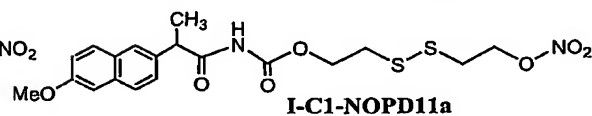
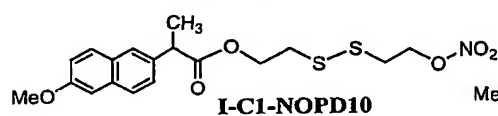
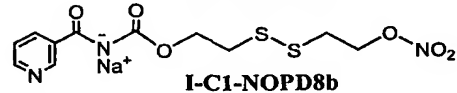
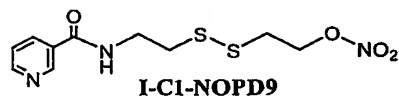
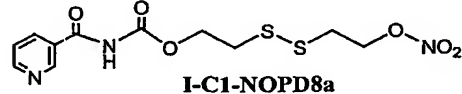
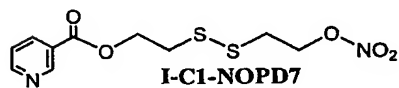
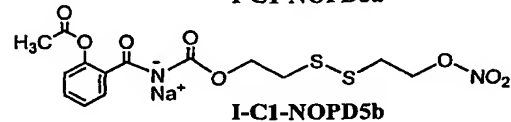
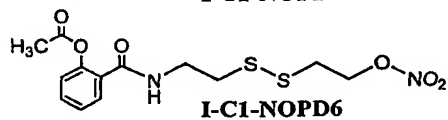
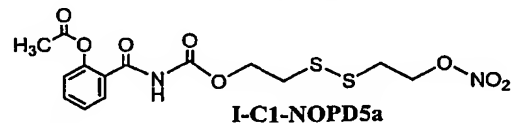
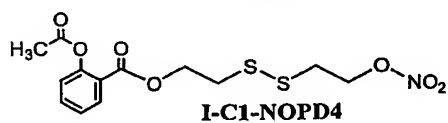
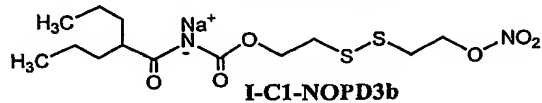
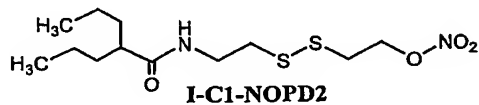
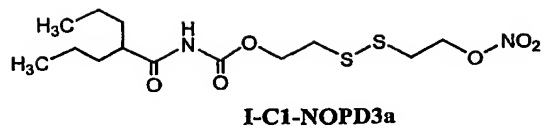
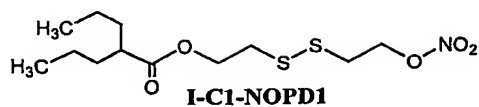
$\text{Y} = \text{O}, \text{NR}^1$ ($\text{R}^1 = \text{H}, \text{Alkyl}, \text{Aralkyl}, \text{Cycloalkyl}$), $(\text{CH}_2)_n\text{C}(=\text{O})$ ($n=1-6$), $(\text{CH}_2)_n\text{CO}_2\text{---}$

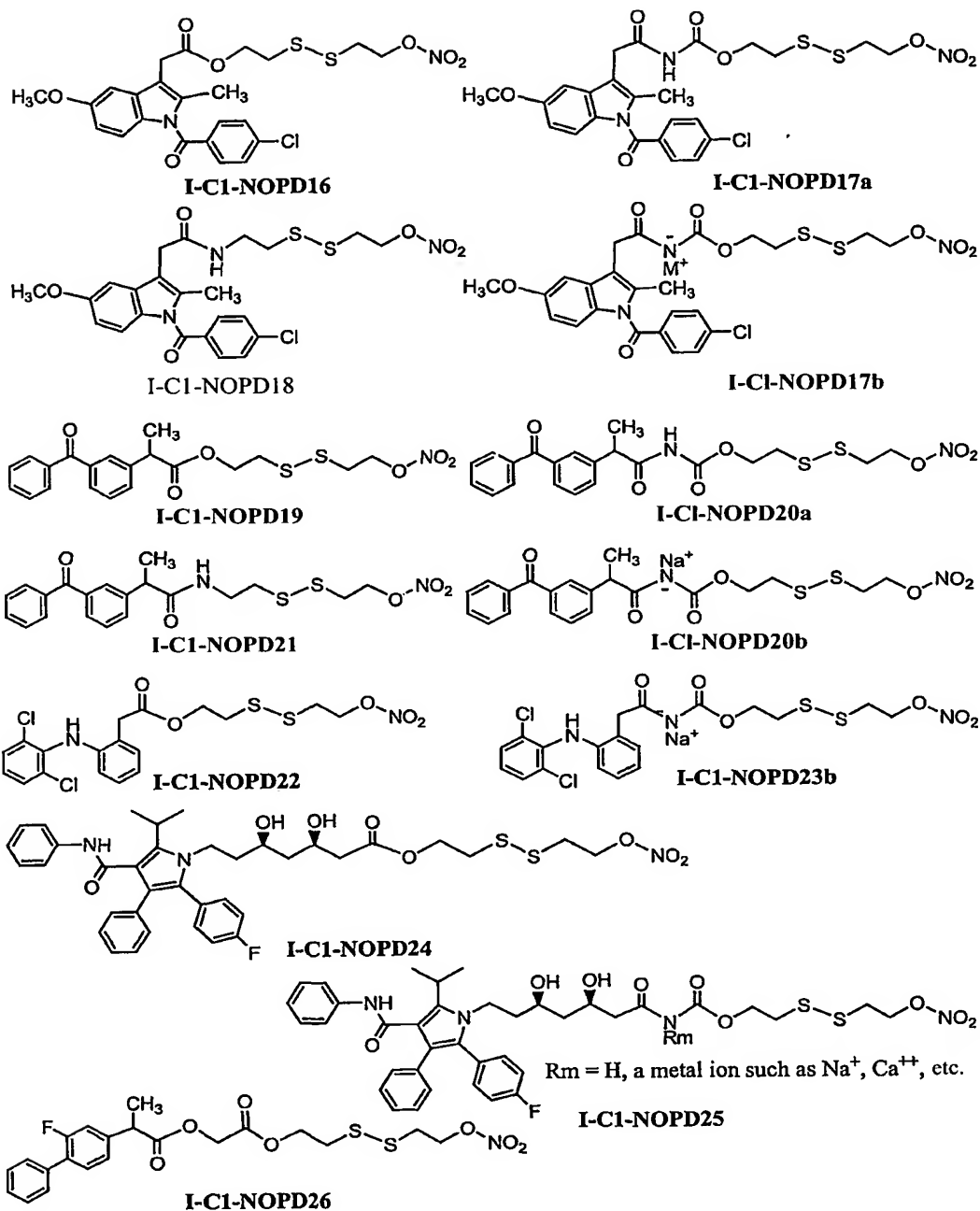
$\text{Z} = \text{C}=\text{O}, \text{SO}_2, \text{P}(=\text{O})\text{YR}^3$ ($\text{R}^3 = \text{H}$ or a metal ion)

$\text{R}^2 = \text{H}$, a bond, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \cdot \text{HCl}$, an Amino acid, or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such as Na^+ , Ca^{2+} , etc.

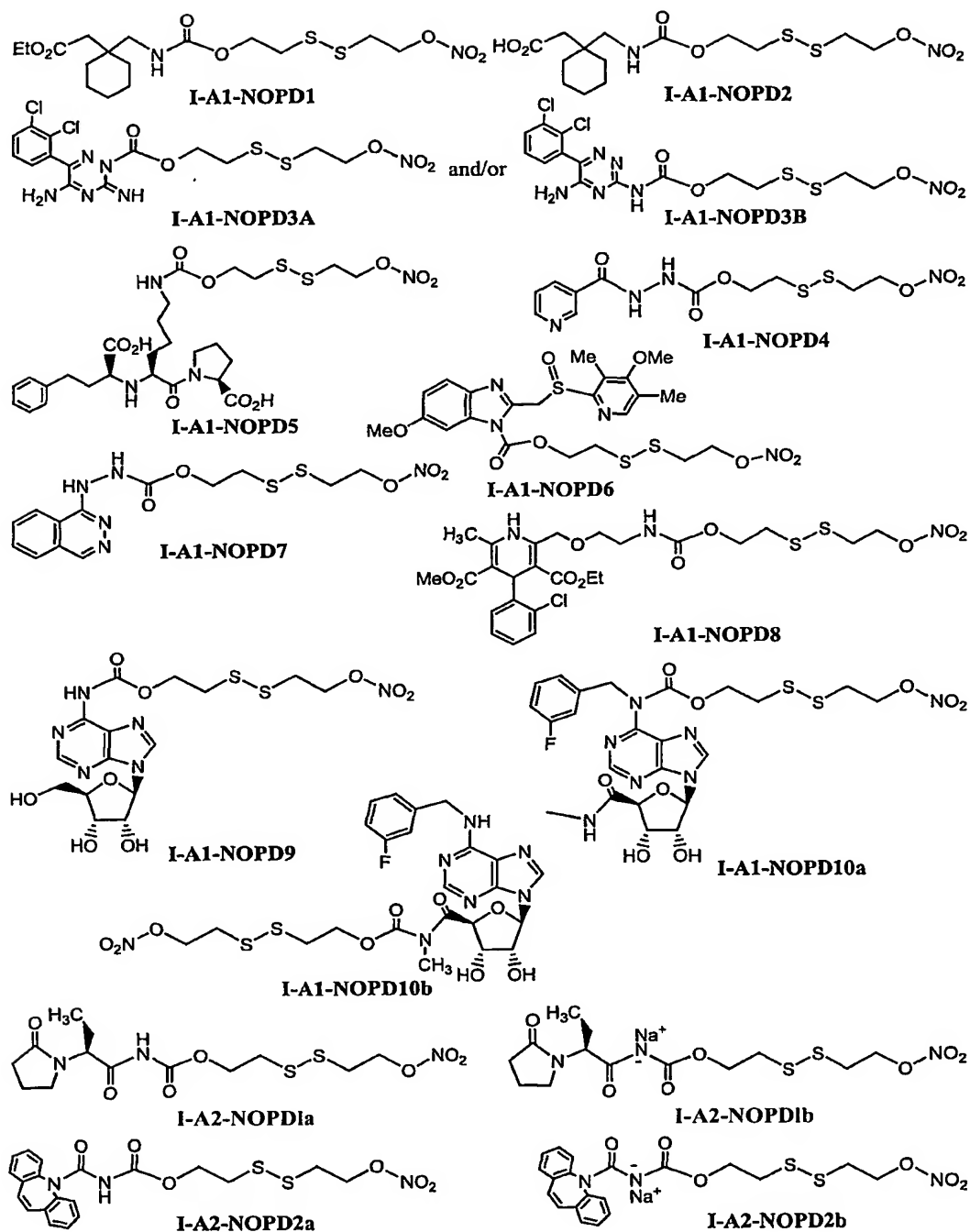
B. NO-releasing Prodrugs

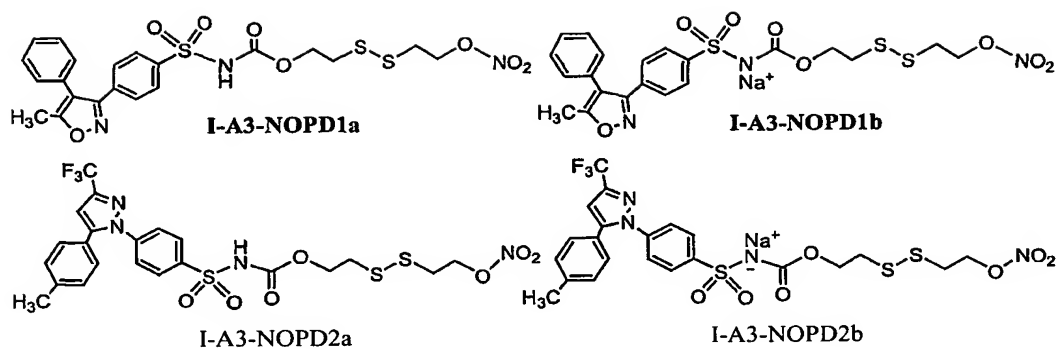
(a) From carboxyl-containing drugs



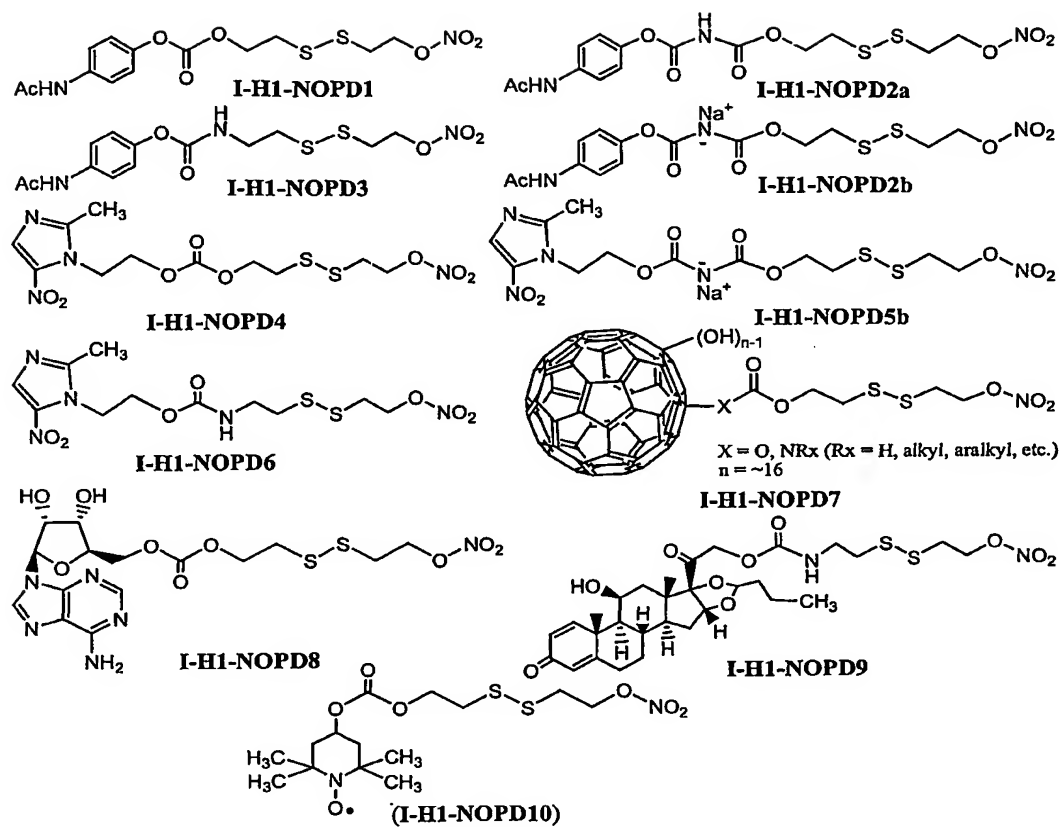


(b) From amino-containing drugs

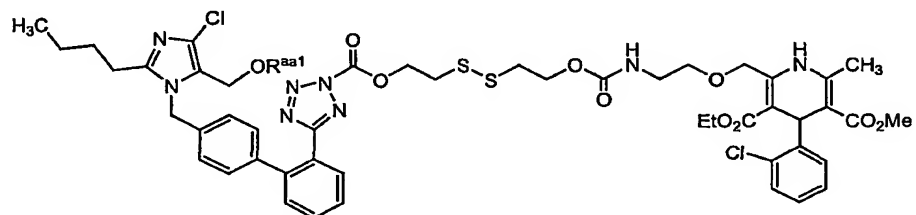
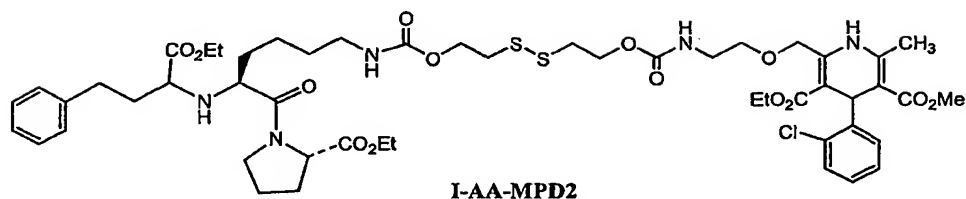
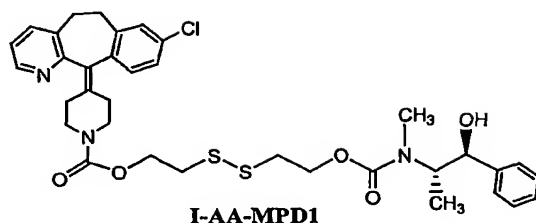




(c) From hydroxyl-containing drugs

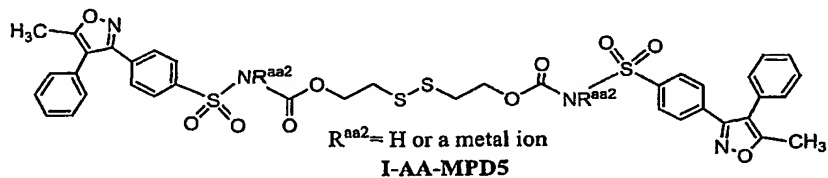
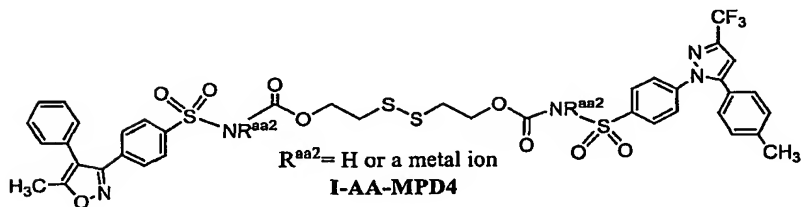


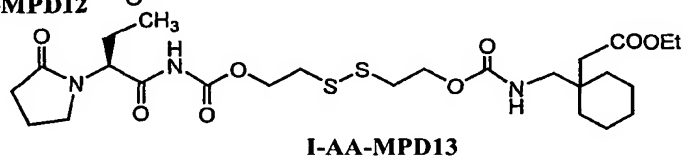
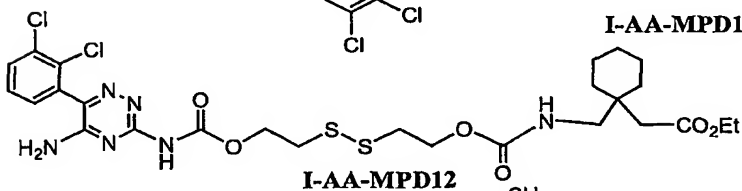
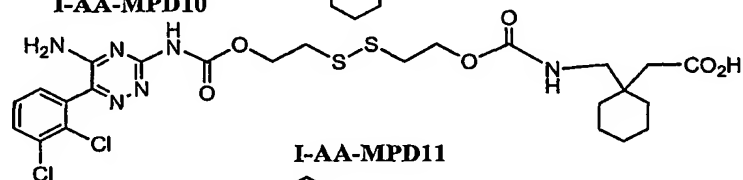
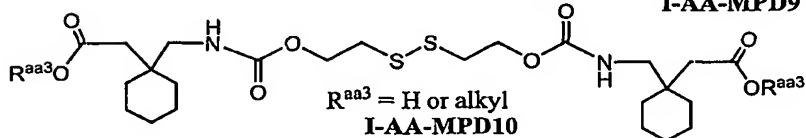
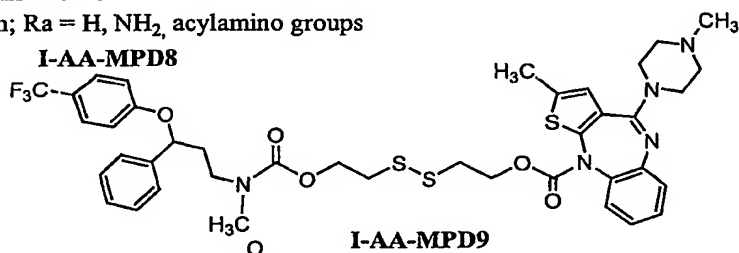
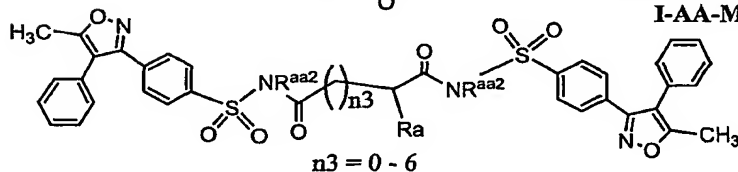
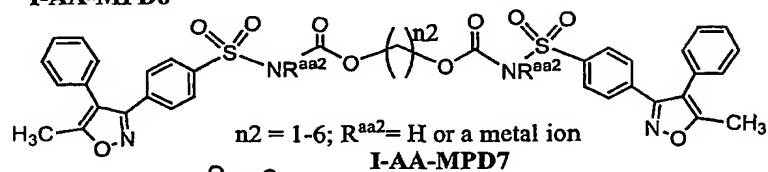
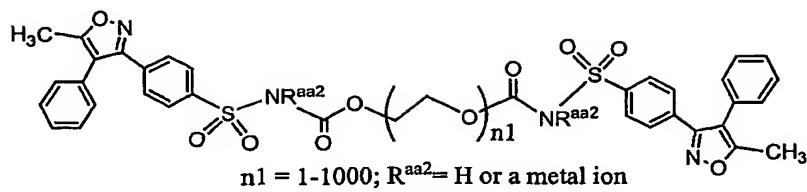
- 5 C. Mutual or Double Prudrugs
- (a) From two amino-containing drugs

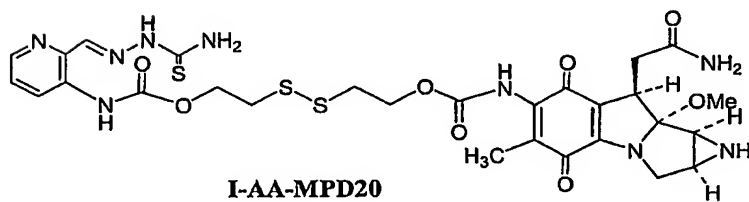
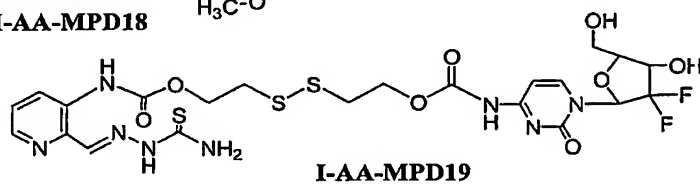
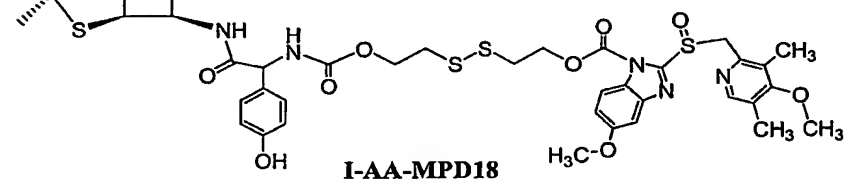
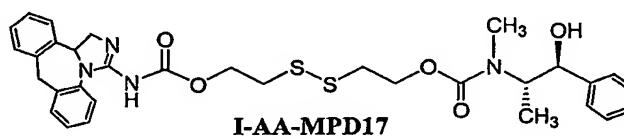
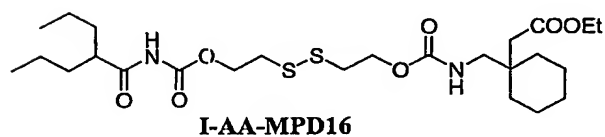
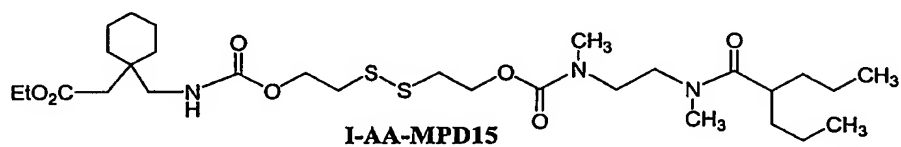
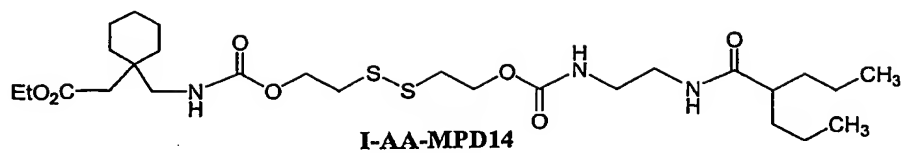


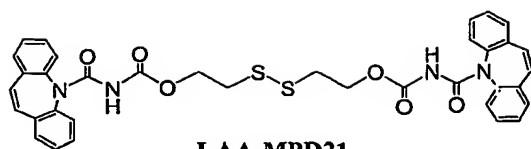
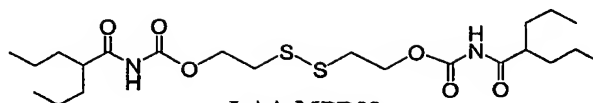
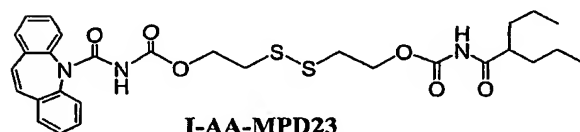
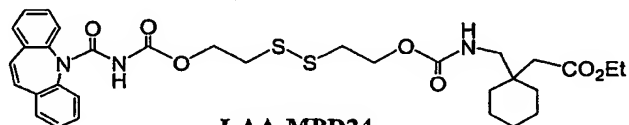
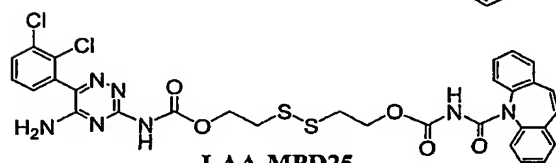
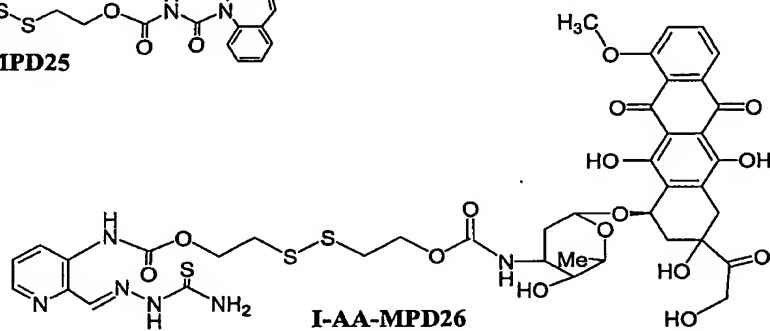
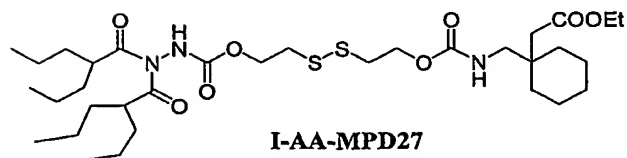
$R^{aa1} = \text{H}, \text{PO}_3\text{H}_2, \text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{NMe}_2, \text{C}(\text{O})\text{CH}_2\text{NR}'_2 \text{ (R' = H or Alkyl)},$
 $\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{NMe}_2, \text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CO}_2\text{H}, \text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{NHCOCH}_2\text{CH}_2\text{CO}_2\text{H},$
 $\text{C}(\text{O})\text{O}(\text{CH}_2)_2\text{NHCO}(\text{CH}_2)_2\text{CO}_2\text{H}, \text{ and } \text{C}(\text{O})\text{CH}_2\text{N}(\text{CH}_2\text{CO}_2\text{H})_2.$

I-AA-MPD3a (Raa1 = H)

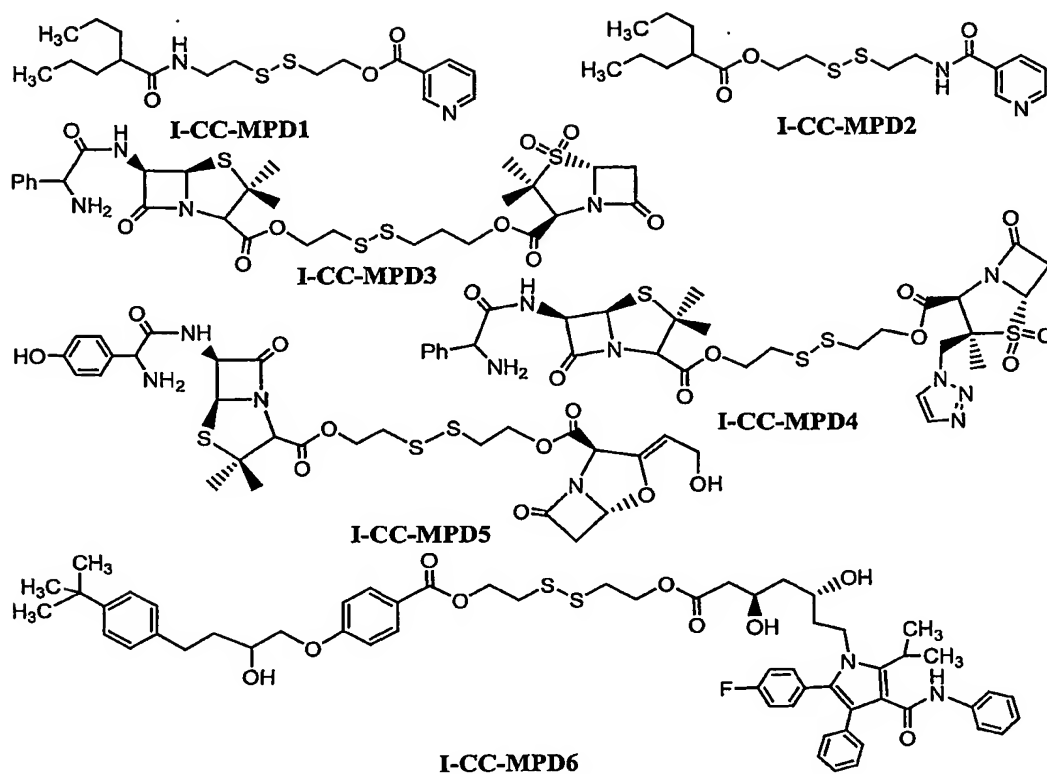




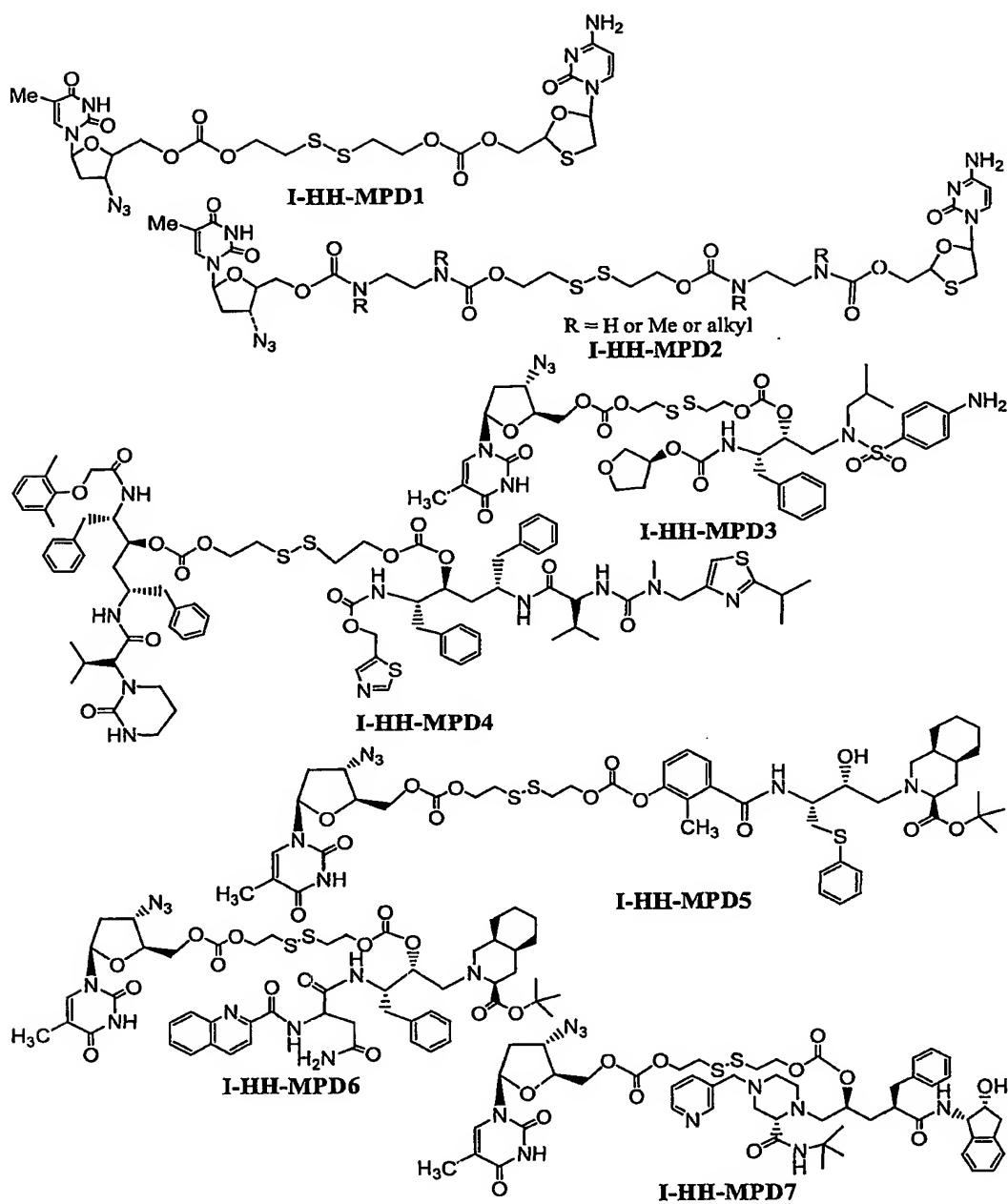


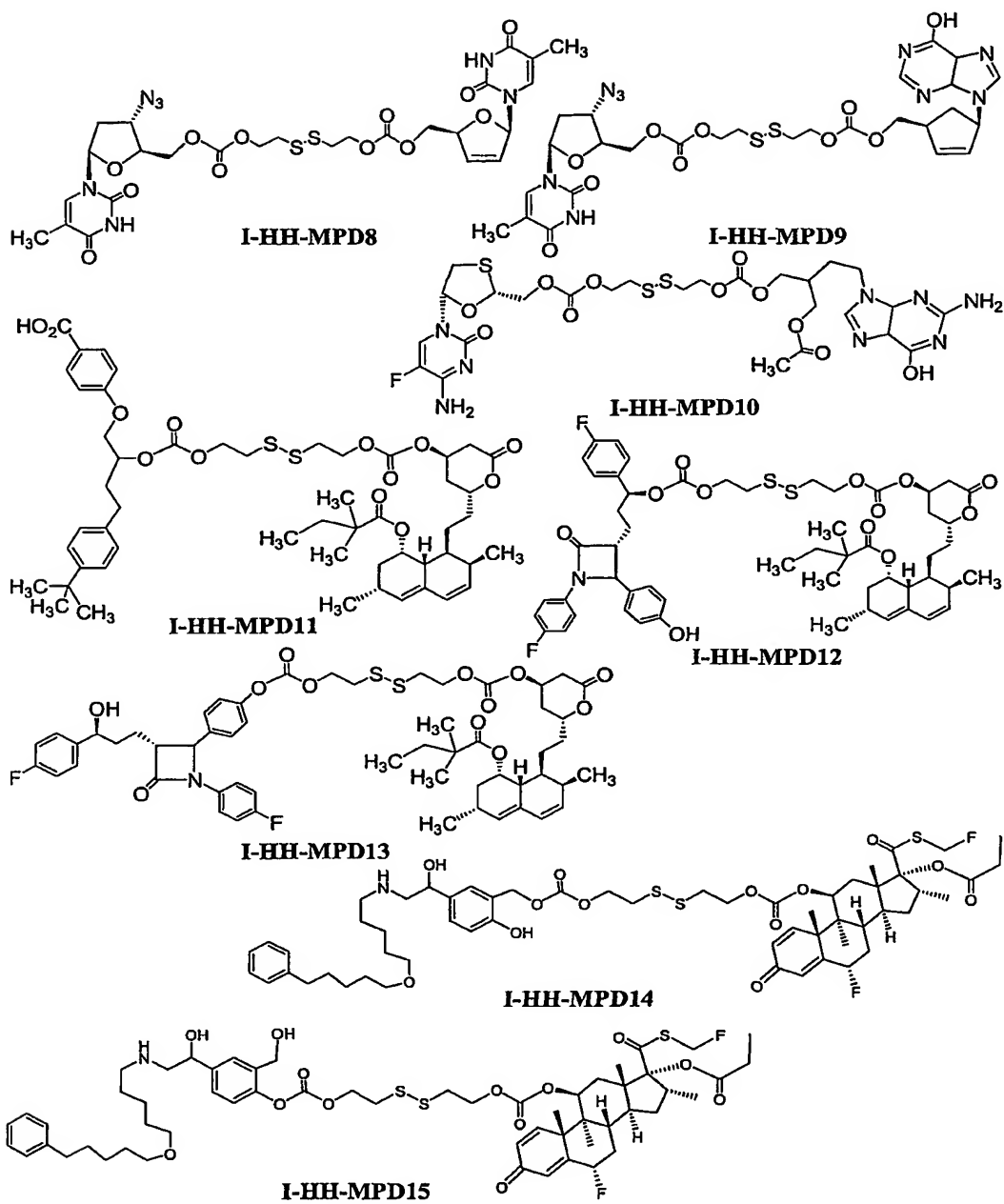
**I-AA-MPD21****I-AA-MPD22****I-AA-MPD23****I-AA-MPD24****I-AA-MPD25****I-AA-MPD26****I-AA-MPD27**

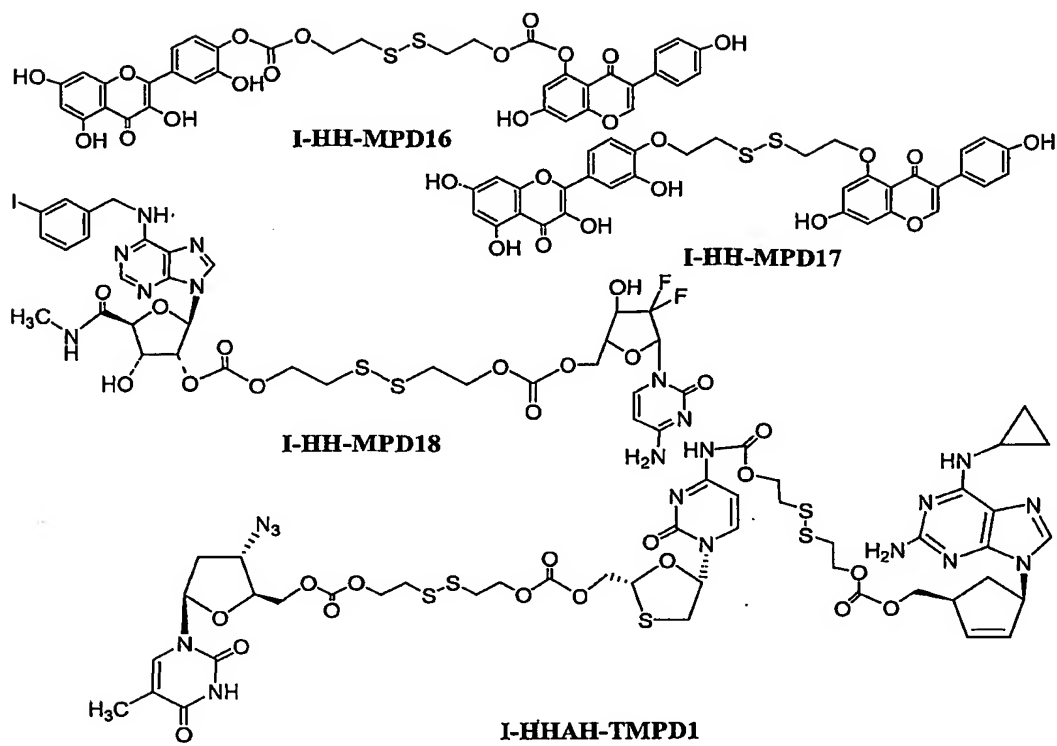
(b) From two carboxyl-containing drugs



(c) From two hydroxyl-containing drugs



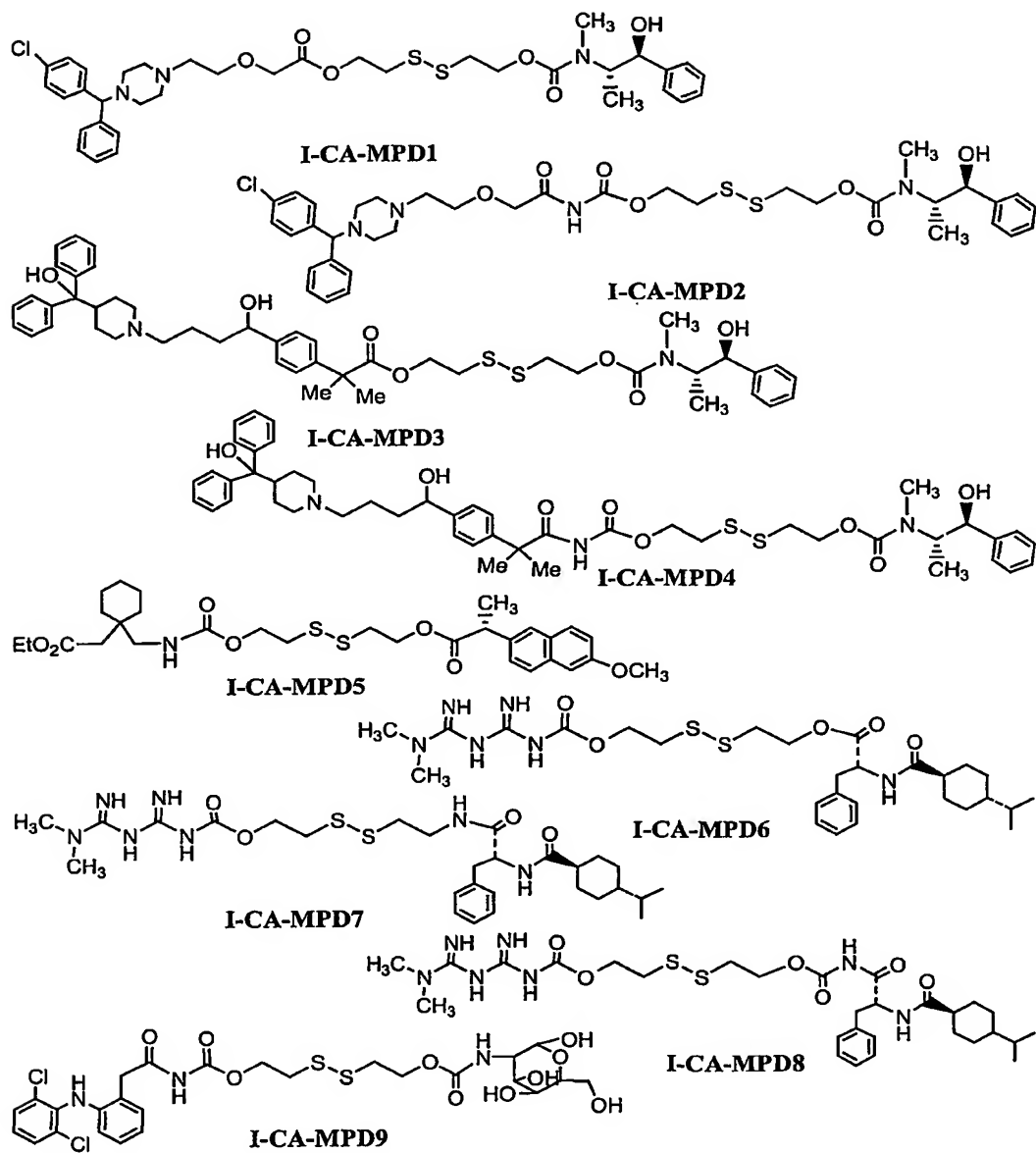


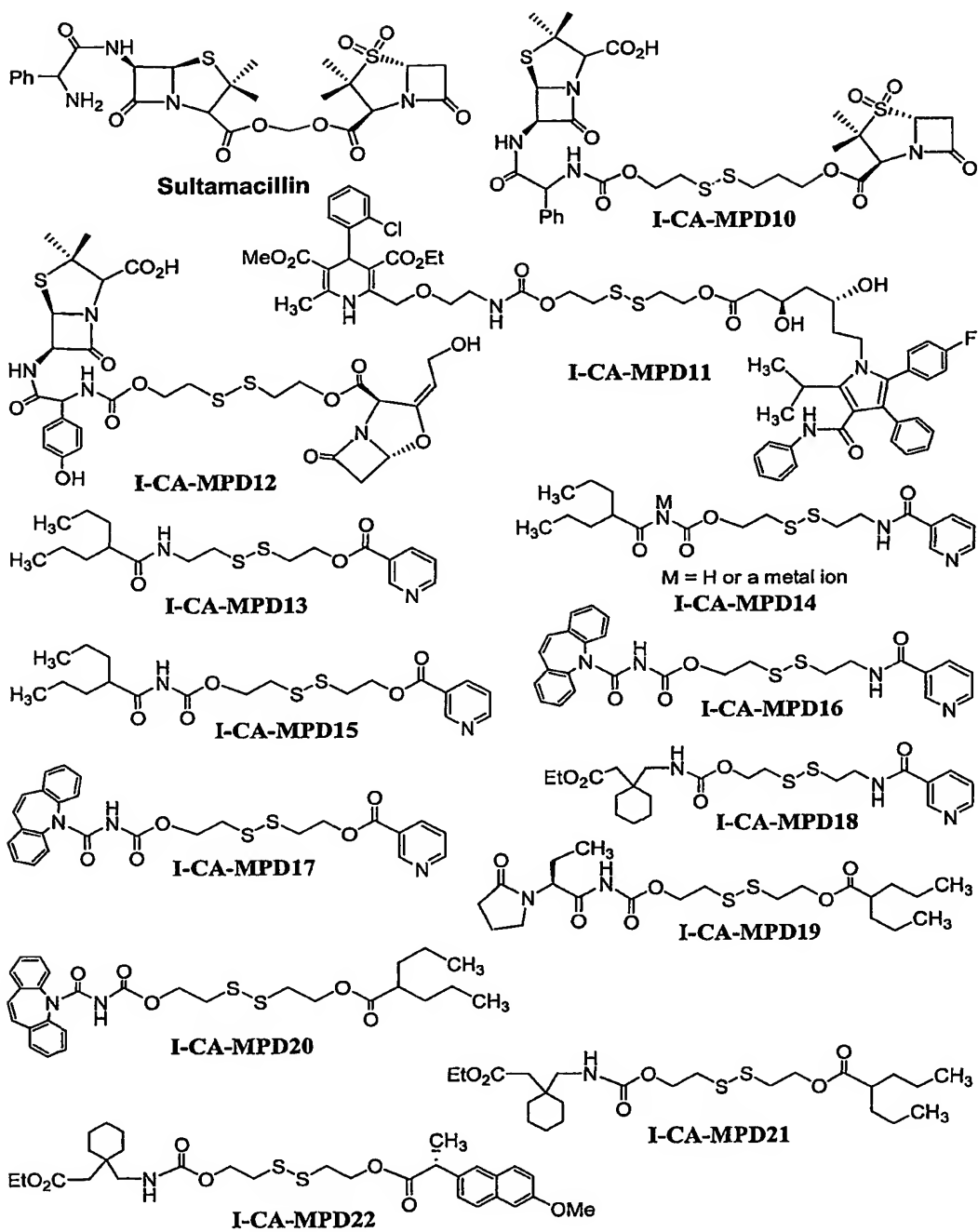


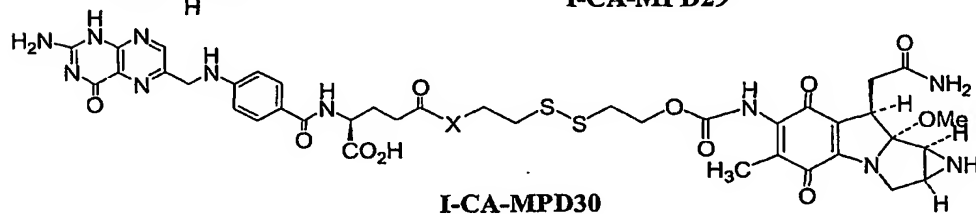
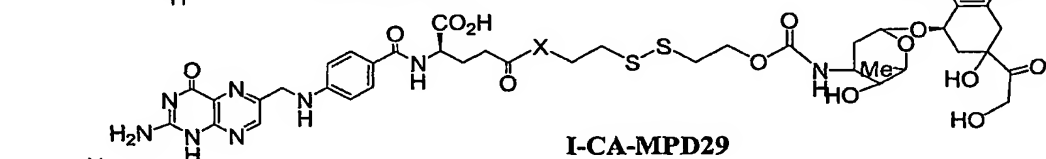
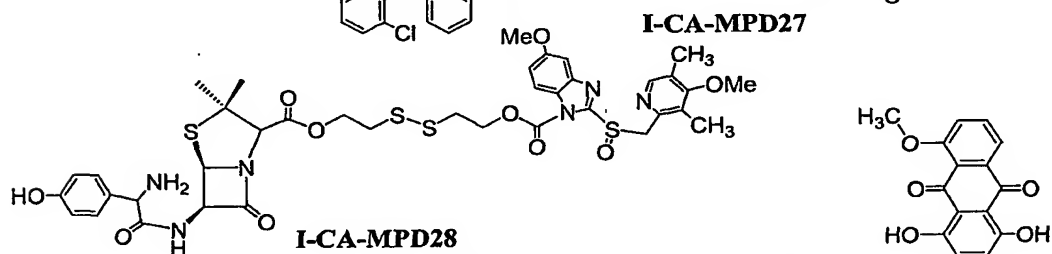
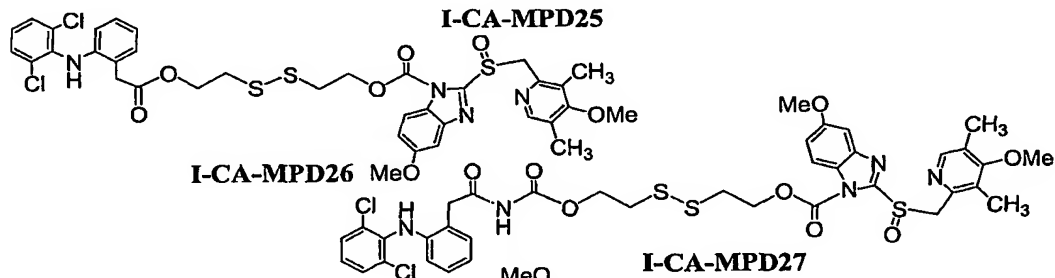
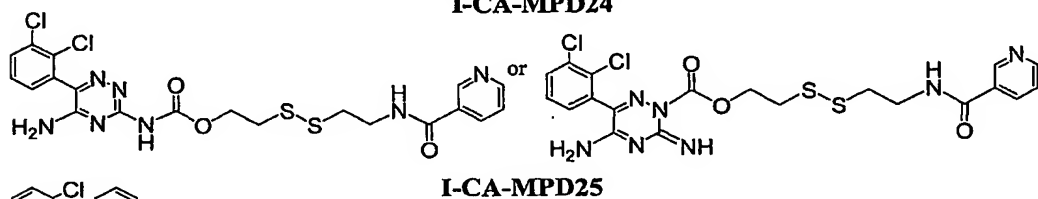
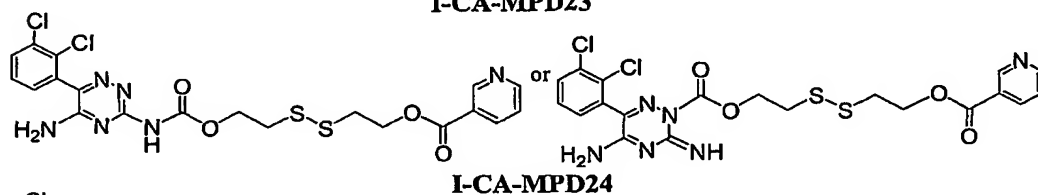
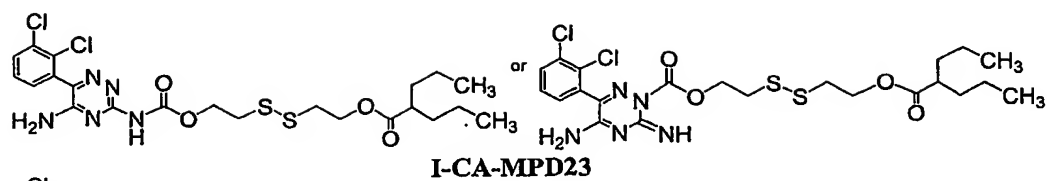
5

10

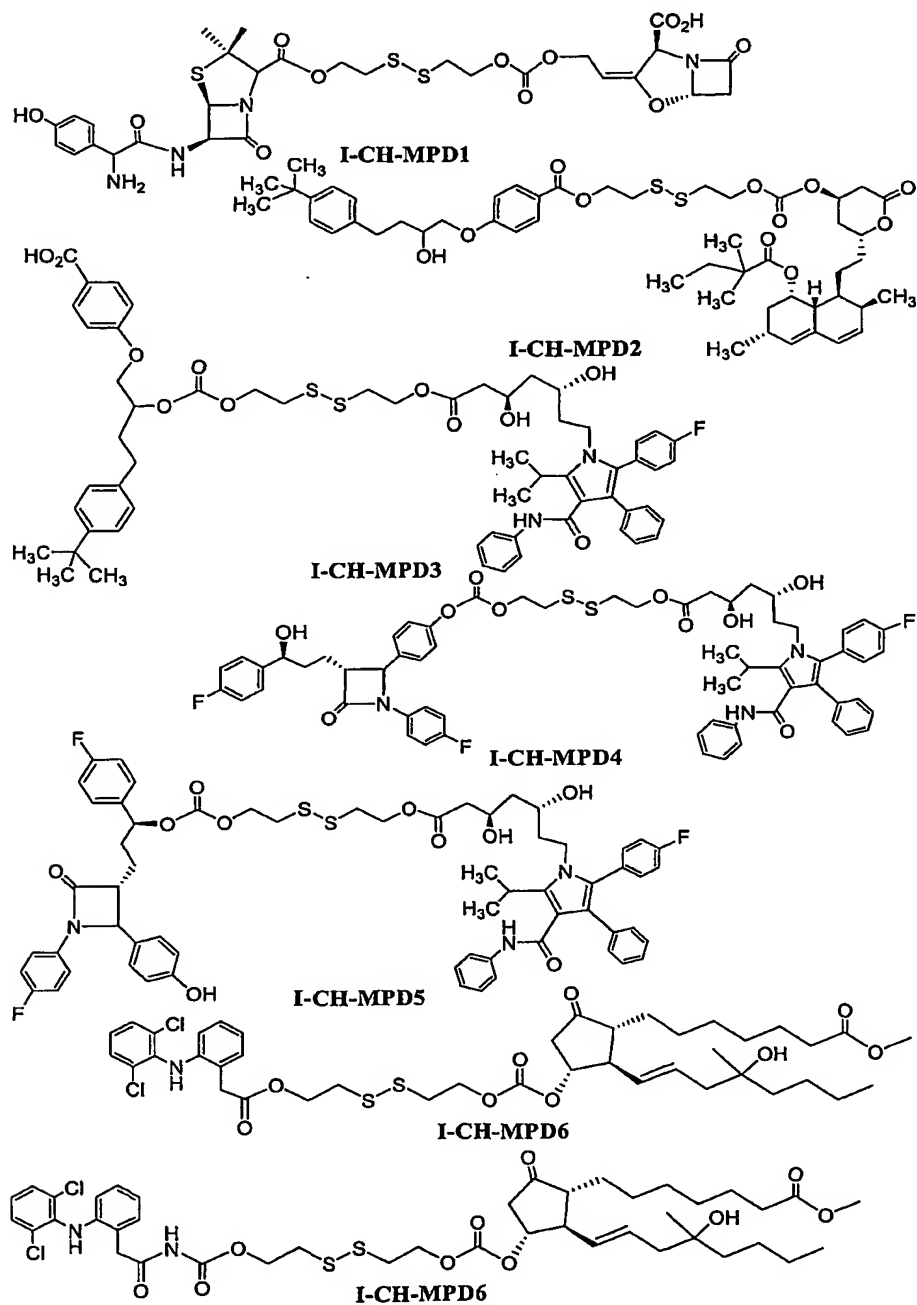
(d) From an amino-containing drug and a carboxyl-containing drug:



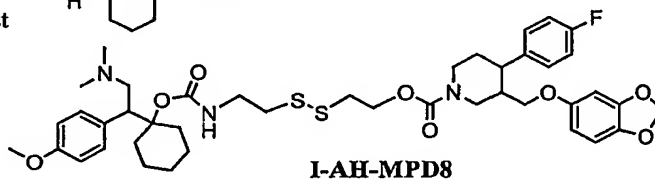
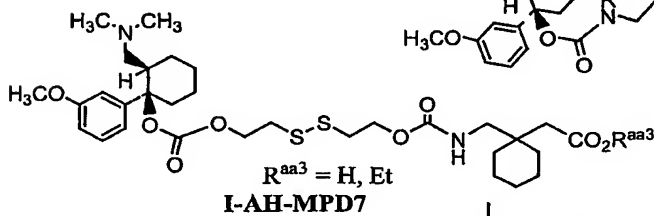
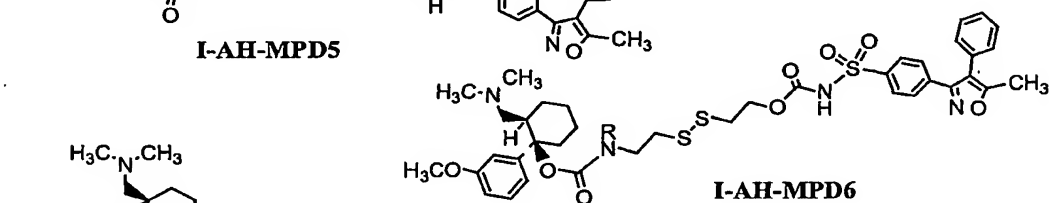
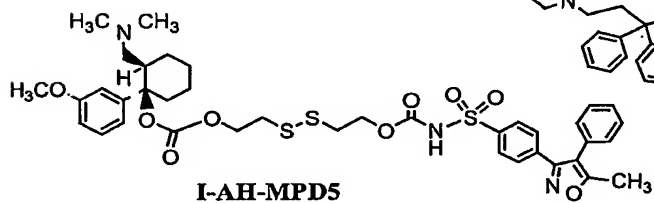
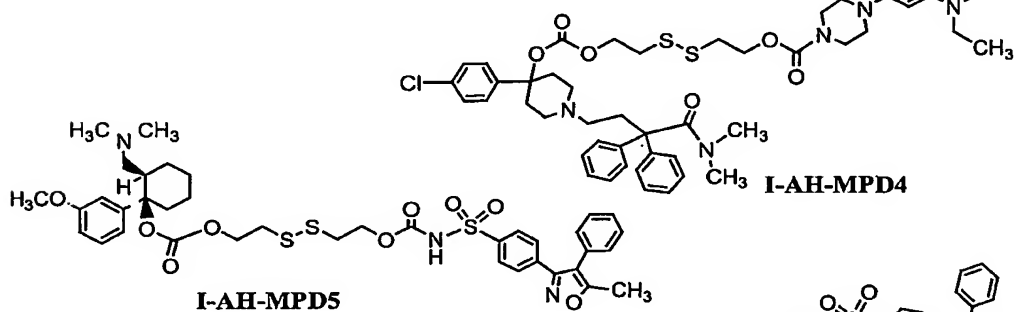
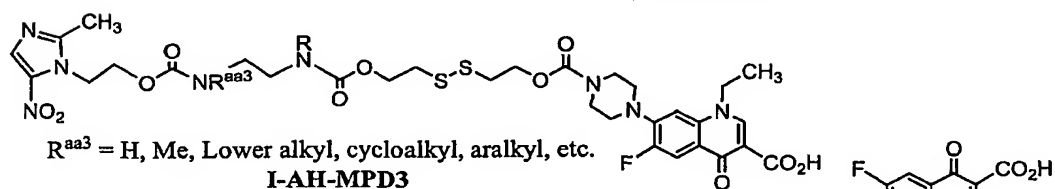
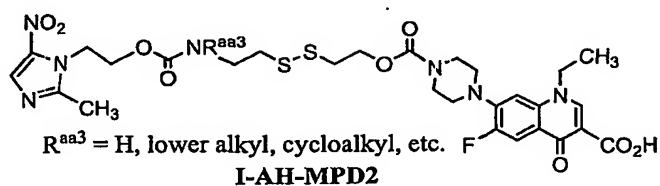
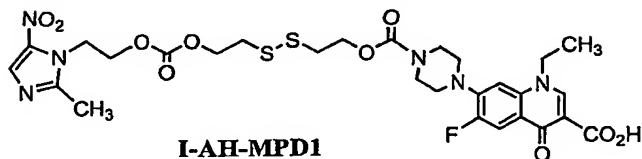


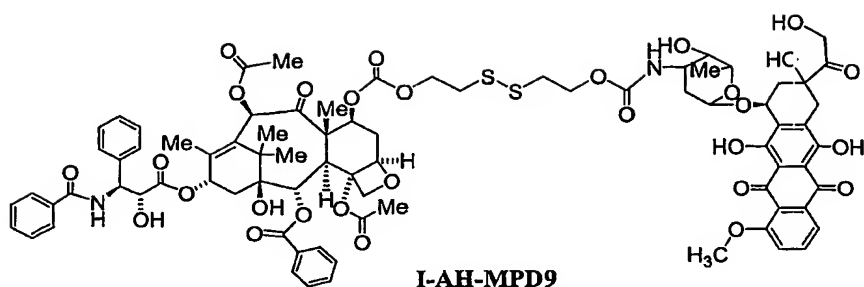
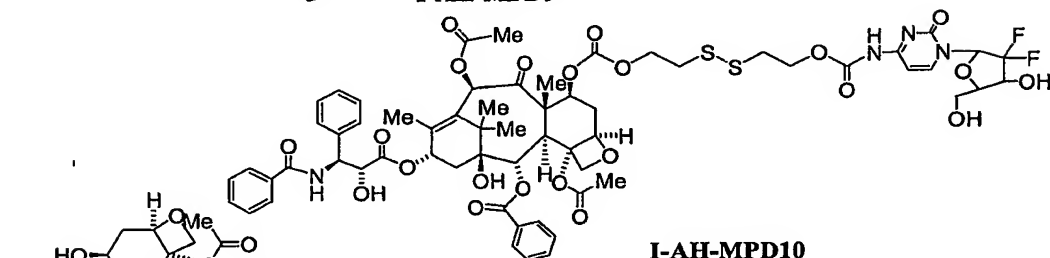
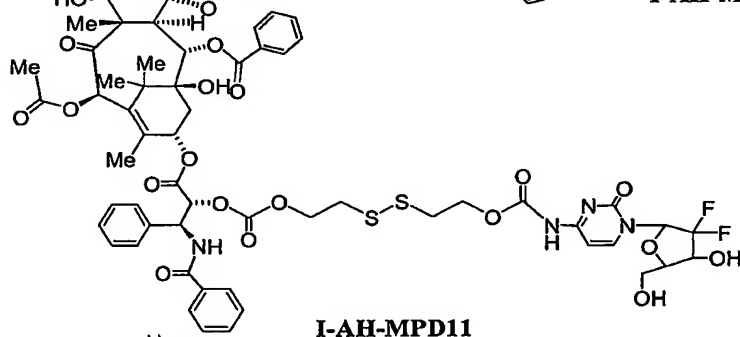
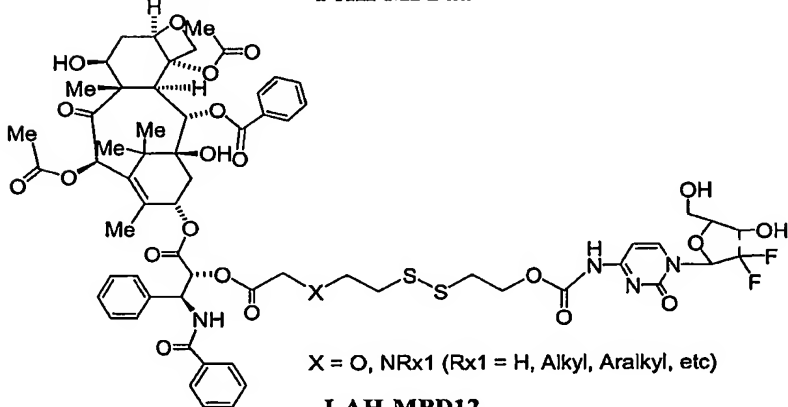


(e) Mutual prodrugs of one carboxyl-containing and one hydroxyl-containing drugs



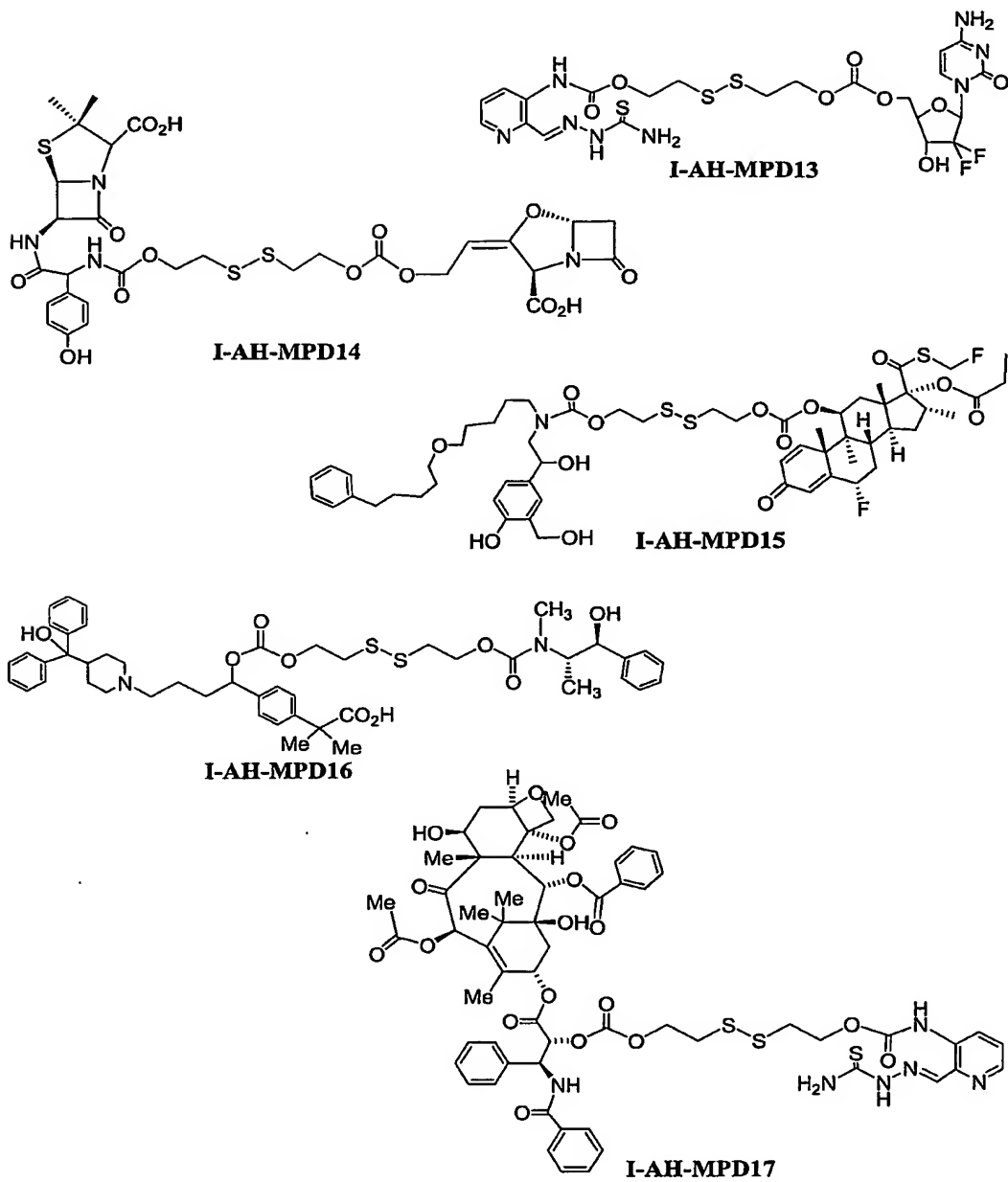
(f) Mutual prodrugs of one amino-containing and one hydroxyl-containing drugs

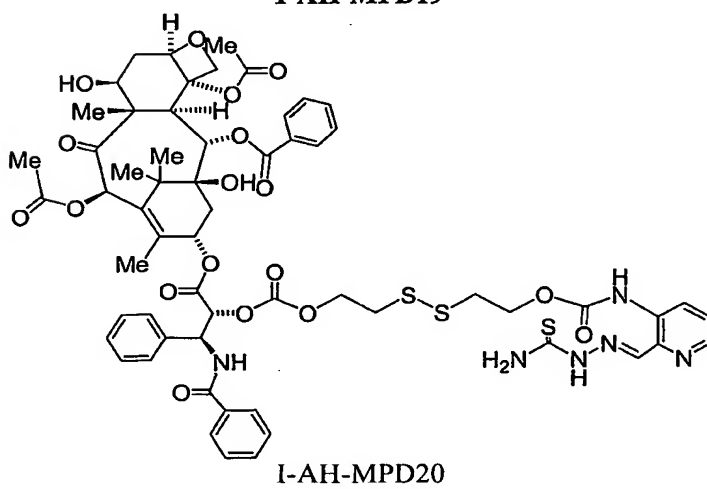
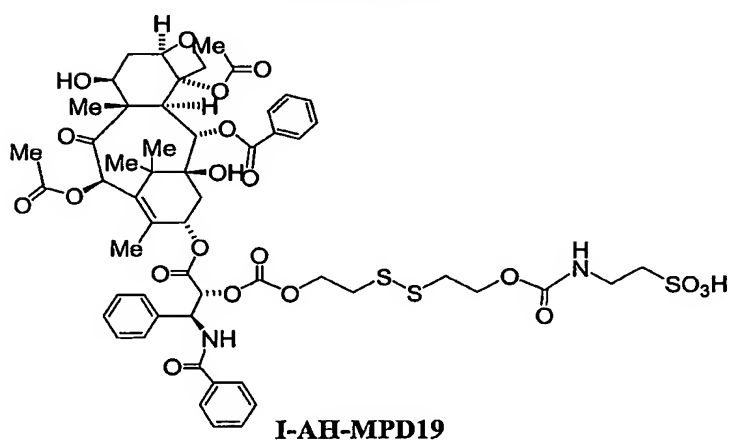
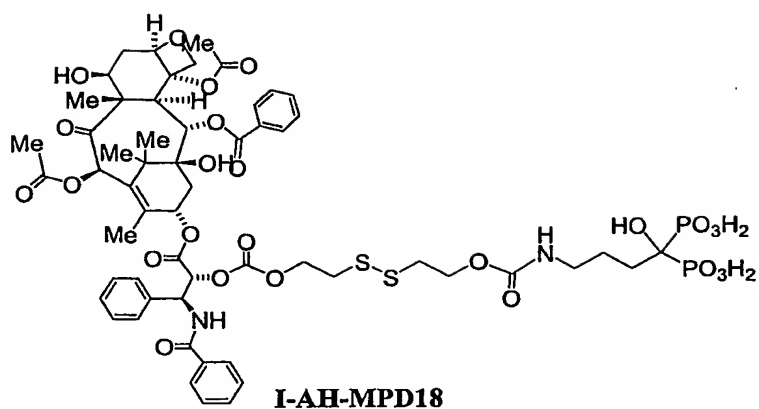


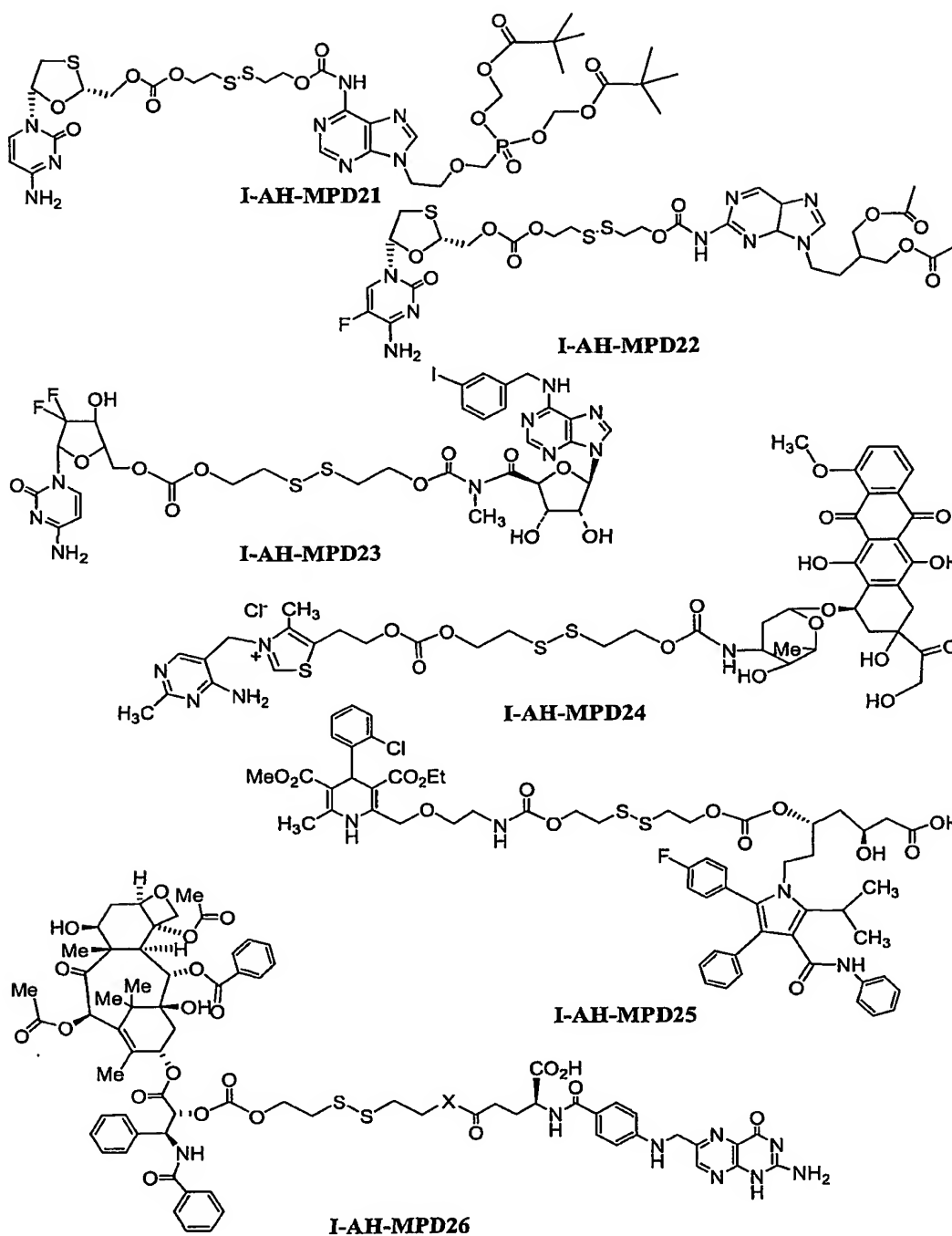
**I-AH-MPD9****I-AH-MPD10****I-AH-MPD11**

X = O, NR_{x1} (R_{x1} = H, Alkyl, Aalkyl, etc)

I-AH-MPD12







An embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

- Another embodiment of the invention is a pharmaceutical composition
- 5 comprising a therapeutically effective amount of the compound of formula I selected from the group consisting of I-C1-PD1, I-C1-PD2, I-C1-PD3, I-C1-PD4, I-C1-PD4a, I-C1-PD4b, I-C1-PD5, I-C1-PD6, I-C1-PD7, I-C1-PD8, I-C1-PD9, I-C1-PD10, I-C1-PD11, I-C1-PD12, I-C1-PD13, I-C1-PD14, I-C1-PD15a, I-C1-PD15b, I-A1-PD1, I-A1-PD2, I-A1-PD3, I-A1-PD4, I-A1-PD5, I-A1-PD6, I-A1-PD7, I-A1-PD8, I-A1-PD9, I-A1-PD10, I-A1-PD11, I-A1-PD12, I-A1-PD13, I-A1-PD14, I-A1-PD15A, I-A1-PD15Aa, I-A1-PD15B, I-A1-PD15Bb, I-A1-PD16, I-A1-PD17, I-A2-PD1, I-A2-PD2, I-A2-PD2b, I-A2-PD3a, I-A2-PD3b, I-A2-PD4, I-A2-PD5, I-A3-PD1, I-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, I-A3-PD5, I-A3-PD6, I-A3-PD7b, I-H1-PD1, I-H1-PD2, I-H1-PD3, I-H1-PD4, I-H1-PD5, I-H1-PD6, I-H1-PD7, I-H1-PD8, I-H1-PD9, I-H1-PD10, I-H1-PD11, I-H1-PD12, I-H1-PD13, I-Taxol-PD1, I-Taxol-PD2, I-Taxol-PD3, I-Taxol-PD4, I-Taxol-PD5, I-Taxol-PD6, I-S23-PD1, I-C1-NOPD1, I-C1-NOPD2, I-C1-NOPD3a, I-C1-NOPD3b, I-C1-NOPD4, I-C1-NOPD5a, I-C1-NOPD5b, I-C1-NOPD6, I-C1-NOPD7, I-C1-NOPD8a, I-C1-NOPD8b, I-C1-NOPD9, I-C1-NOPD10, I-C1-NOPD11a, I-C1-NOPD13, I-C1-NOPD14a, I-C1-NOPD14b, I-C1-NOPD15b, I-C1-NOPD16, I-C1-NOPD17a, I-C1-NOPD17b, I-C1-NOPD18, I-C1-NOPD19, I-C1-NOPD20a, I-C1-NOPD20b, I-C1-NOPD21, I-C1-NOPD22, I-C1-NOPD23b, I-C1-NOPD24, I-C1-NOPD25, I-C1-NOPD26, I-A1-NOPD1, I-A1-NOPD2, I-A1-NOPD3A, I-A1-NOPD3B, I-A1-NOPD4, I-A1-NOPD5, I-A1-NOPD6, I-A1-NOPD7, I-A1-NOPD8, I-A1-NOPD9, I-A1-NOPD10a, I-A1-NOPD10b, I-A2-NOPD1a, I-A2-NOPD1b, I-A2-NOPD2a, I-A2-NOPD2b, I-A3-NOPD1a, I-A3-NOPD1b, I-A3-NOPD2a, I-A3-NOPD2b, I-H1-NOPD1, I-H1-NOPD2a, I-H1-NOPD2b, I-H1-NOPD3, I-H1-NOPD4, I-H1-NOPD5b, I-H1-NOPD6, I-H1-NOPD7, I-H1-NOPD8, I-H1-NOPD9, I-H1-NOPD10, I-AA-MPD1, I-AA-MPD2, I-AA-MPD3a, I-AA-MPD4, I-AA-MPD5, I-AA-MPD6, I-AA-MPD7, I-AA-MPD8, I-AA-MPD9, I-AA-MPD10, I-AA-MPD11, I-AA-MPD12, I-AA-MPD13, I-AA-MPD14, I-AA-MPD15, I-AA-MPD16, I-AA-MPD17, I-AA-MPD18, I-AA-MPD19, I-AA-MPD20, I-AA-MPD21, I-AA-MPD22, I-AA-
 - 10
 - 15
 - 20
 - 25
 - 30

MPD23, 1-AA-MPD24, 1-AA-MPD25, 1-AA-MPD26, 1-AA-MPD27, 1-CC-MPD1, 1-CC-MPD2, 1-CC-MPD3, 1-CC-MPD4, 1-CC-MPD5, 1-CC-MPD6, 1-HH-MPD1, 1-HH-MPD2, 1-HH-MPD3, 1-HH-MPD4, 1-HH-MPD5, 1-HH-MPD6, 1-HH-MPD7, 1-HH-MPD8, 1-HH-MPD9, 1-HH-MPD10, 1-HH-MPD11, 1-HH-MPD12, 1-HH-MPD13, 1-HH-MPD14, 1-HH-MPD15, 1-HH-MPD16, 1-HH-MPD17, 1-HH-MPD18, 1-HHAH-TMPD1, 1-CA-MPD1, 1-CA-MPD2, 1-CA-MPD3, 1-CA-MPD4, 1-CA-MPD5, 1-CA-MPD6, 1-CA-MPD7, 1-CA-MPD8, 1-CA-MPD9, 1-CA-MPD10, 1-CA-MPD11, 1-CA-MPD12, 1-CA-MPD13, 1-CA-MPD14, 1-CA-MPD15, 1-CA-MPD16, 1-CA-MPD17, 1-CA-MPD18, 1-CA-MPD19, 1-CA-MPD20, 1-CA-MPD21, 1-CA-MPD22, 1-CA-MPD23, 1-CA-MPD24, 1-CA-MPD25, 1-CA-MPD26, 1-CA-MPD27, 1-CA-MPD28, 1-CA-MPD29, 1-CA-MPD30, 1-AH-MPD1, 1-AH-MPD2, 1-AH-MPD3, 1-AH-MPD4, 1-AH-MPD5, 1-AH-MPD6, 1-AH-MPD7, 1-AH-MPD8, 1-AH-MPD9, 1-AH-MPD10, 1-AH-MPD11, 1-AH-MPD12, 1-AH-MPD13, 1-AH-MPD14, 1-AH-MPD15, 1-AH-MPD16, 1-AH-MPD17, 1-AH-MPD18, 1-AH-MPD19, 1-AH-MPD20, 1-AH-MPD21, 1-AH-MPD22, 1-AH-MPD23, 1-AH-MPD24, 1-AH-MPD25, 1-AH-MPD26, 1-CH-MPD1, 1-CH-MPD2, 1-CH-MPD3, 1-CH-MPD4, 1-CH-MPD5, and 1-CH-MPD6 or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

An embodiment of the invention is a method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the pharmaceutical composition comprising the compound of formula I.

25

30

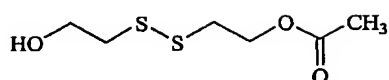
5

10

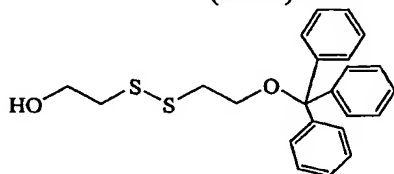
15

20

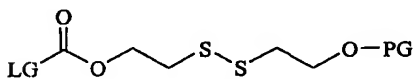
Another embodiment of the invention is the below listed novel intermediates:



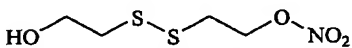
2-((2-Hydroxyethyl)disulfanyl)ethyl acetate
(LI-1a)



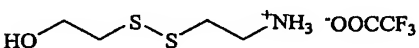
2-((2-(Trityloxy)ethyl)disulfanyl)ethanol
(LI-1c)



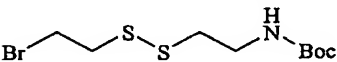
(LI-1xy)



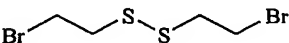
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2b)



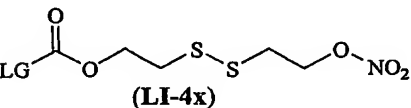
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2c.TFA)



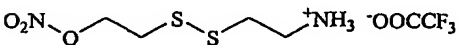
tert-Butyl 2-((2-bromoethyl)-
disulfanyl)ethyl carbamate (LI-2e)



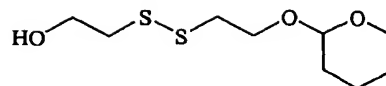
1,2-Bis(2-bromoethyl)disulfane (LI-3a)



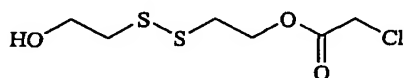
(LI-4x)



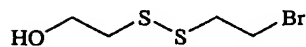
2-((2-Aminoethyl)disulfanyl)ethyl
nitrate.acid salt (LI-5.TFA)



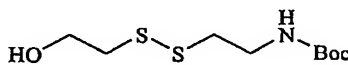
2-((2-(Tetrahydro-2*H*-pyran-2-
yloxy)ethyl)disulfanyl)ethanol (LI-1b)



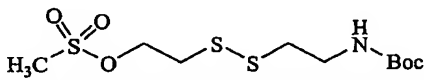
2-((2-Hydroxyethyl)disulfanyl)ethyl
2-chloroacetate (LI-1d)



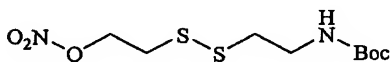
2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)



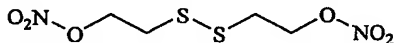
tert-Butyl 2-((2-hydroxyethyl)disulfanyl)-
ethyl carbamate (LI-2c)



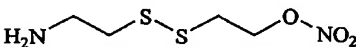
2-((2-(*tert*-Butoxycarbonylamino)ethyl)-
disulfanyl)ethyl methanesulfonate (LI-2d)



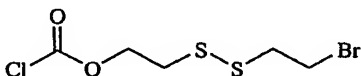
tert-Butyl 2-((2-(nitrooxy)ethyl)-
disulfanyl)ethyl carbamate (LI-2f)



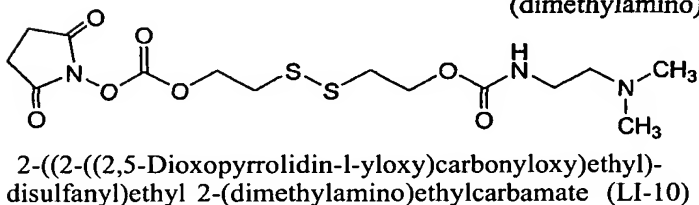
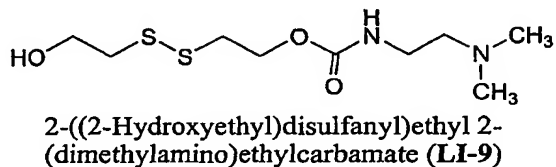
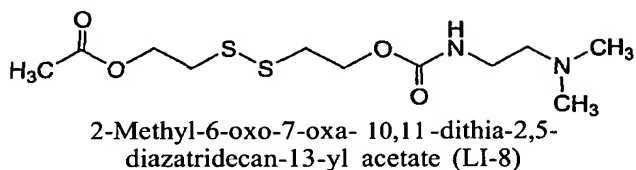
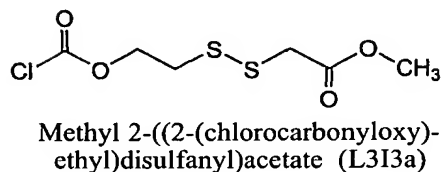
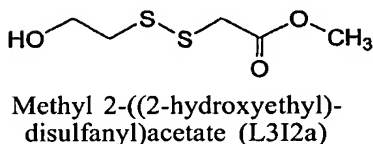
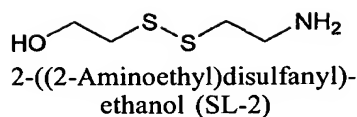
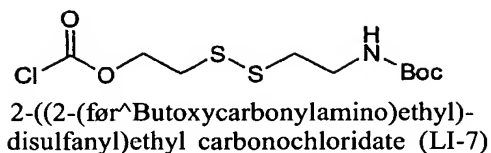
2,2'-Disulfanediyldis(ethane-2,1-diyl)
dinitrate (LI-3b)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)



2-((2-Bromoethyl)disulfanyl)ethyl
carbonochloridate (LI-6)



Another embodiment of the invention is use of the above listed novel

5 intermediates in the processes for the preparation of compounds of formula I;

Further embodiments include methods of preparation and methods of use of compounds of formula (I) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is process for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the process comprises

10 of:

monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give a corresponding monoprotected intermediate,

conversion of the corresponding monoprotected intermediate to an activated formyl intermediate by treating with phosgene or its equivalent, and
reaction of the activated formyl intermediate with an appropriate amino- or hydroxy containing D¹ to give the corresponding compound of formula I.

5 Another embodiment of the invention is a process for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the process comprises of:

- converting carboxy containing D¹ into an activated intermediate comprising acyl halide, imidazolide or isocyanate, and
- 10 -reacting the activated intermediate with a linker intermediate to obtain the compound of formula I.

In another embodiment, the invention is a process in which the monoprotected intermediate is LIIx, and the activated formyl intermediate is LIIxy.

Another embodiment of the invention is a process for preparation of compounds
15 of formula (I), wherein D₂ is NO₂ or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated D¹ with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) in a suitable solvent in presence of a suitable coupling agent.

Another embodiment of the invention is a process for preparation of compounds
20 of formula (I), wherein D² is NO₂ or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) into its formyl halide or imidazolide (LI-4x) by using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable amino- or hydroxy-containing drug in suitable solvent in presence of a suitable base.

25 Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D² is NO₂ or pharmaceutically acceptable salt thereof, wherein the process comprises, mixing/reacting a selectively protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base.

Another embodiment of the invention is a process for preparation of mutual prodrugs of compounds of formula (I), or pharmaceutically acceptable salts thereof, wherein a process comprises,

- A) monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LI-Ix,
- B) reaction of formyl linker intermediate LI-Ixy with amino or hydroxyl containing drug (D¹) to obtain the prodrug of formula I with free hydroxyl group on the linker,
- C) conversion of the intermediate obtained in the step B into activated formyl halide or imidazolide derivative, and
- D) reaction of the intermediate obtained in the step C with the drug D² to obtain the mutual prodrug of formula I.

Further embodiments of the invention are processes for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the processes comprise of the steps that are generally depicted in the schemes 1-23.

- Further embodiments include the pharmaceutical composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

- Another embodiment of the invention is use of compounds of formula (I) or pharmaceutically acceptable salt thereof, in the treatment of disease conditions originally treatable by the corresponding free drug(s).

- It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material, process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. The contents of the articles, patents, and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

Yet another embodiment of the invention is a compound of formula I containing an amino-containing therapeutic agent selected from the group consisting of: I-AA-MPD1, I-AA-MPD2, I-AA-MPD3, and I-AA-MPD4.

Another embodiment of the invention is double prodrug of formula (I) selected from the group consisting of: I-AA-MPD5, I-AA-MPD6, I-AA-MPD7, and I-AA-MPD8.

The present invention also provides mutual prodrugs of formula (I) selected from the group consisting of: I-CA-MPD1, I-CA-MPD2, I-CA-MPD3, I-CA-MPD4, I-CA-MPD5, I-CA-MPD6, I-CA-MPD7, I-CA-MPD8, I-CA-MPD9, I-CA-MPD10, I-CA-MPD11, I-CA-MPD12, I-CA-MPD13, I-CA-MPD14, I-CA-MPD15, I-CA-MPD16, I-CA-MPD17, I-CA-MPD18, I-CA-MPD19, I-CA-MPD20, I-CA-MPD21, I-CA-MPD22, I-CA-MPD23, I-CA-MPD24, I-CA-MPD25, I-CA-MPD26, I-CA-MPD27, I-CA-MPD28, I-CA-MPD29, and I-CA-MPD30.

In another embodiment, the invention provides compounds of formula (I) selected from the group of mutual prodrugs made from amino-containing therapeutic agent and a hydroxyl-containing therapeutic agent such as: I-AH-MPD1, I-AH-MPD2, I-AH-MPD3, I-AH-MPD4, I-AH-MPD5, I-AH-MPD6, I-AH-MPD7, I-AH-MPD8, I-AH-MPD9, I-AH-MPD10, I-AH-MPD11, I-AH-MPD12, I-AH-MPD13, I-AH-MPD14, I-AH-MPD15, I-AH-MPD16, I-AH-MPD17, I-AH-MPD18, I-AH-MPD19, I-AH-MPD20, I-AH-MPD21, I-AH-MPD22, I-AH-MPD23, I-AH-MPD24, I-AH-MPD25, and I-AH-MPD26.

Yet another embodiment of the invention relates to compounds of formula (I) of mutual prodrugs made from a hydroxyl-containing therapeutic agent and a hydroxyl-containing therapeutic agent such as: I-HH-MPD1, I-HH-MPD2, I-HH-MPD3, I-HH-MPD4, I-HH-MPD5, I-HH-MPD6, I-HH-MPD7, I-HH-MPD8, I-HH-MPD9, I-HH-MPD10, I-HH-MPD11, I-HH-MPD12, I-HH-MPD13, I-HH-MPD14, I-HH-MPD15, I-HH-MPD16, I-HH-MPD17, and I-HH-MPD18.

The present invention also provides compounds of formula (I) containing water-soluble prodrugs of insoluble or sparingly-soluble therapeutic agents such as: I-H1-PD1, I-H1-PD2, I-H1-PD3, I-H1-PD4, I-H1-PD5, I-H1-PD6, I-H1-PD7, I-H1-PD8, I-H1-PD9, I-H1-PD10, I-H1-PD11, I-H1-PD12, I-H1-PD13, I-A1-PD1, I-A1-PD2, I-A1-PD3, I-A1-PD4, I-A1-PD5, I-A1-PD6, I-A1-PD7, I-A1-PD8, I-A1-PD9, I-A1-PD10, I-A1-PD11, I-A1-PD12, I-A1-PD13, I-A1-PD14, I-A1-PD15A, I-A1-PD1Aa, I-A1-PD15B, I-A1-

PD15Bb, I-A1-PD16, I-A1-PD17, I-A2-PD1, I-A2-PD2, I-A2-PD2b, I-A2-PD3a, I-A2-PD3b, I-A2-PD4, I-A2-PD5, I-A3-PD1, I-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, I-A3-PD5, I-A3-PD6, I-A3-PD7b, I-H1-PD1, I-H1-PD2, I-H1-PD3, I-H1-PD4, I-H1-PD5, I-H1-PD6, I-H1-PD7, I-H1-PD8, I-H1-PD9, I-H1-PD10, I-H1-PD11, I-H1-PD12, I-H1-PD13, I-Taxol-PD1, I-Taxol-PD2, I-Taxol-PD3, I-Taxol-PD4, I-Taxol-PD5, I-Taxol-PD6, and I-S23-PD1.

Another embodiment of the invention relates to the compounds of formula (I), selected from the group of NO-releasing prodrugs consisting of: I-C1-NOPD1, I-C1-NOPD2, I-C1-NOPD3a, I-C1-NOPD3b, I-C1-NOPD4, I-C1-NOPD5a, I-C1-NOPD5b, I-C1-NOPD6, I-C1-NOPD7, I-C1-NOPD8a, I-C1-NOPD8b, I-C1-NOPD9, I-C1-NOPD10, I-C1-NOPD11a, I-C1-NOPD13, I-C1-NOPD14a, I-C1-NOPD14b, I-C1-NOPD15b, I-C1-NOPD16, I-C1-NOPD17a, I-C1-NOPD17b, I-C1-NOPD18, I-C1-NOPD19, I-C1-NOPD20a, I-C1-NOPD20b, I-C1-NOPD21, I-C1-NOPD22, I-C1-NOPD23b, I-C1-NOPD24, I-C1-NOPD25, I-C1-NOPD26, I-A1-NOPD1, I-A1-NOPD2, I-A1-NOPD3A, I-A1-NOPD3B, I-A1-NOPD4, I-A1-NOPD5, I-A1-NOPD6, I-A1-NOPD7, I-A1-NOPD8, I-A1-NOPD9, I-A1-NOPD10a, I-A1-NOPD10b, I-A2-NOPD1a, I-A2-NOPD1b, I-A2-NOPD2a, I-A2-NOPD2b, I-A3-NOPD1a, I-A3-NOPD1b, I-A3-NOPD2a, I-A3-NOPD2b, I-H1-NOPD1, I-H1-NOPD2a, I-H1-NOPD2b, I-H1-NOPD3, I-H1-NOPD4, I-H1-NOPD5b, I-H1-NOPD6, I-H1-NOPD7, I-H1-NOPD8, I-H1-NOPD9, I-H1-NOPD10.

Another aspect of the invention provides the use of the compounds of formula (I) in combination with a compound used to treat cardiovascular diseases selected from the group consisting of: beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, HMGCoA reductase inhibitors, aspirin or nitrooxy derivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers. Suitable drugs are described in the literature such as the Merck Index, IDdb, Prous Science's Integrity®, Prous Science Drugs of the Future™, The Ensemble® and the like.

Another aspect of the invention provides the use of the pharmaceutical compositions containing compounds of formula (I) in combination with a compound, used to treat other diseases such as cardiovascular diseases, selected from beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics,

HMGCoA reductase inhibitors, aspirin or nitrooxy derivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers. Pharmaceutical compositions containing two or more of compounds of the invention can be used for the purpose of combination therapy. These pairs of compounds of invention can be from the same therapeutic area or from different therapeutic areas for treating one or more diseases or conditions.

The compounds of the invention, which have one or more asymmetric carbon atoms, can exist as the optically pure enantiomers, pure diastereomers, enantiomer racemic mixtures, diastereomer racemic mixtures, racemates or racemate mixtures. Within the scope of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and at least another pharmaceutically active compound. The pharmaceutically active compound can be from the same or different therapeutic areas for treating one or more disease condition(s) together with one or more pharmaceutically acceptable carriers, vehicles or diluents.

Further embodiments include methods of use of compounds of formula (I) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated drug with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate in a suitable solvent in presence of a suitable coupling agent. Another embodiment of the invention is a compound or intermediate generated in the above methods and processes.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyethyl)dithio)ethyl nitrate into its formyl halide or imidazolide by

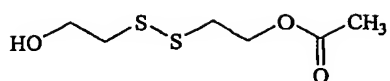
using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable drug in suitable solvent in presence of a suitable base.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, wherein the process comprises,
5 mixing/reacting a selectively protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (or its acid salt) in a suitable solvent in presence of a suitable coupling agent and/or base.

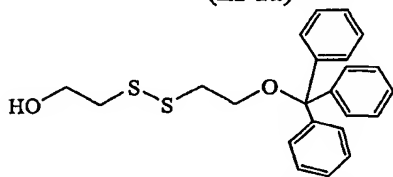
Another embodiment of the invention comprises the novel intermediates formed in the preparation of present invention. Further embodiments include a pharmaceutical
10 composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is processes for the preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, as well as the
15 starting materials and intermediates involved as depicted in schemes 1-23.

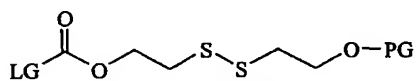
Another embodiment of the invention the novel intermediates obtained in the preparation of compounds of formula I, wherein the intermediates are selected from:



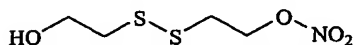
2-((2-Hydroxyethyl)disulfanyl)ethyl acetate
(LI-1a)



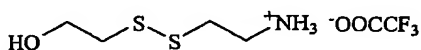
2-((2-(Trityloxy)ethyl)disulfanyl)ethanol
(LI-1c)



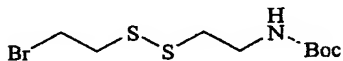
(LI-1xy)



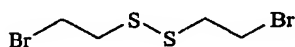
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2b)



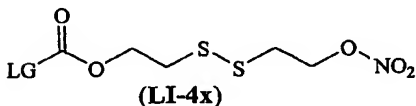
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2c.TFA)



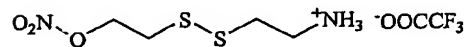
tert-Butyl 2-((2-bromoethyl)-
disulfanyl)ethylcarbamate (LI-2e)



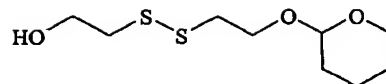
1,2-Bis(2-bromoethyl)disulfane (LI-3a)



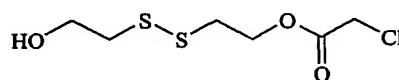
(LI-4x)



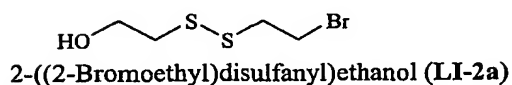
2-((2-Aminoethyl)disulfanyl)ethyl
nitrate.acid salt (LI-5.TFA)



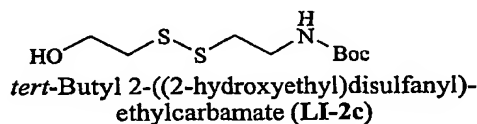
2-((2-(Tetrahydro-2*H*-pyran-2-
yloxy)ethyl)disulfanyl)ethanol (LI-1b)



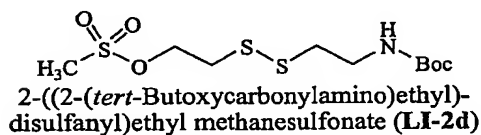
2-((2-Hydroxyethyl)disulfanyl)ethyl
2-chloroacetate (LI-1d)



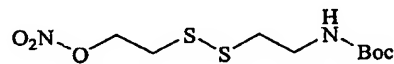
2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)



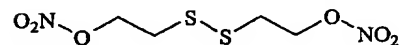
tert-Butyl 2-((2-hydroxyethyl)disulfanyl)-
ethylcarbamate (LI-2c)



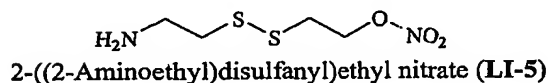
2-((2-(*tert*-Butoxycarbonylamino)ethyl)-
disulfanyl)ethyl methanesulfonate (LI-2d)



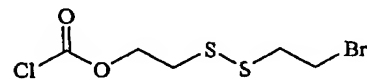
tert-Butyl 2-((2-(nitrooxy)ethyl)-
disulfanyl)ethylcarbamate (LI-2f)



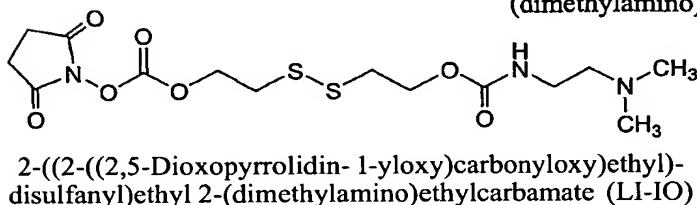
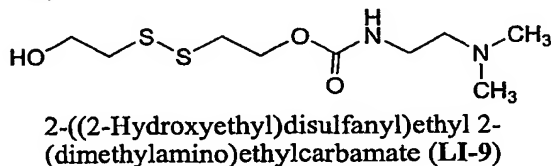
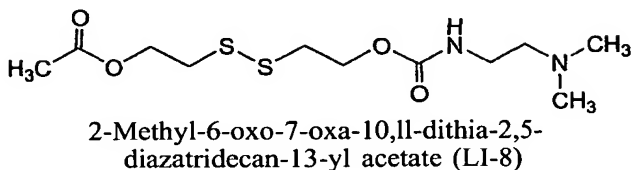
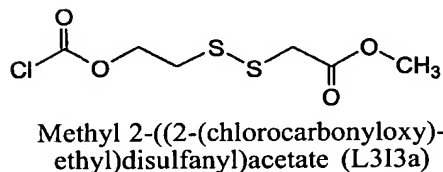
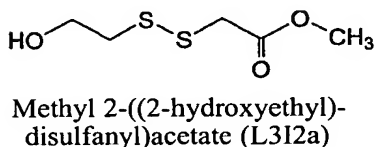
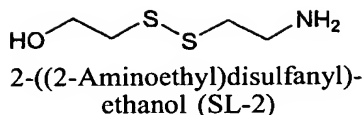
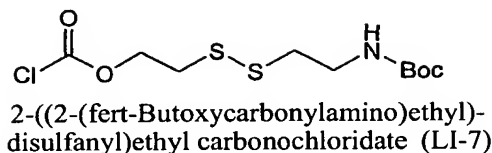
2,2'-Disulfanediybis(ethane-2,1-diyl)
dinitrate (LI-3b)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)



2-((2-Bromoethyl)disulfanyl)ethyl
carbonochloridate (LI-6)



Another embodiment of the invention is use of compounds of formula (I) or pharmaceutically acceptable salts thereof, in the treatment of disease conditions originally treatable by the corresponding free drugs.

- 5 Another embodiment of the invention includes but not limited to a pharmaceutical composition comprising the compounds of formula (I), or pharmaceutically acceptable salt thereof, selected from the group of NO-releasing prodrugs described herein, or more pharmaceutically acceptable carriers, vehicles or diluents.

- 10 It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material,

process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. The contents of the articles, patents, and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

POTENTIAL EXAMPLES OF MUTUAL PRODRUGS/CODRUGS:

Mutual prodrugs made from an amino-containing therapeutic agent and another amino-containing therapeutic agent:

A Mutual Prodrug of desloratadine and pseudoephedrine (I-AA-MPD1) is proposed as a potential treatment option for seasonal allergic rhinitis (SAR). Desloratadine (an active metabolite of loratadine) is a new, non-sedating, long-acting histamine antagonist and has been shown effective in the treatment of nasal and non-nasal symptoms associated with SAR. Pseudoephedrine is an oral decongestant.

A Mutual Prodrug of amlodipine (Pfizer's Norvasc®) and lisinopril (Zeneca's Zestril®) (I-AA-MPD2) is proposed as a potential treatment option for hypertension and congestive heart failure. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent. Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor and is used for the treatment of hypertension and congestive heart failure. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of these drugs.

A Mutual Prodrug of amlodipine (Pfizer's Norvasc®) and losartan (Merck's Cozaar®) (I-AA-MPD3a) is proposed as a potential treatment option for mild to moderate hypertension. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent. Losartan potassium is an angiotensin II blocker and is used for the treatment of hypertension. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of these drugs.

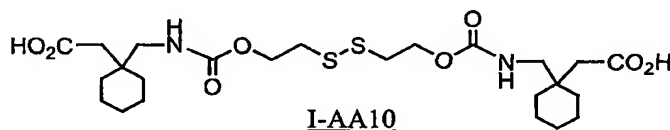
Examples of mutual prodrugs and double prodrugs of valdecoxib and celecoxib containing a disulfide linker are: I-AA-MPD4 and I-AA-MPD5.

Examples of double prodrugs of valdecoxib or celecoxib containing non-disulfide linkers: I-AA-MPD6, I-AA-MPD7, I-AA-MPD8.

5 A Mutual Prodrug of fluoxetine (Lilly's Prozac®) and olanzapine (Lilly's Zyprexa®) (I-AA-MPD9) is proposed for potential treatment of patients with Bipolar disorder. Fluoxetine and Olanzapine are used in combination to treat patients with bipolar disorder while being spared the treatment-emergent mania that such patients often get on antidepressant monotherapy.

Example of double prodrug of gabapentin is proposed as potential antiepileptic agent: I-AA-MPD10.

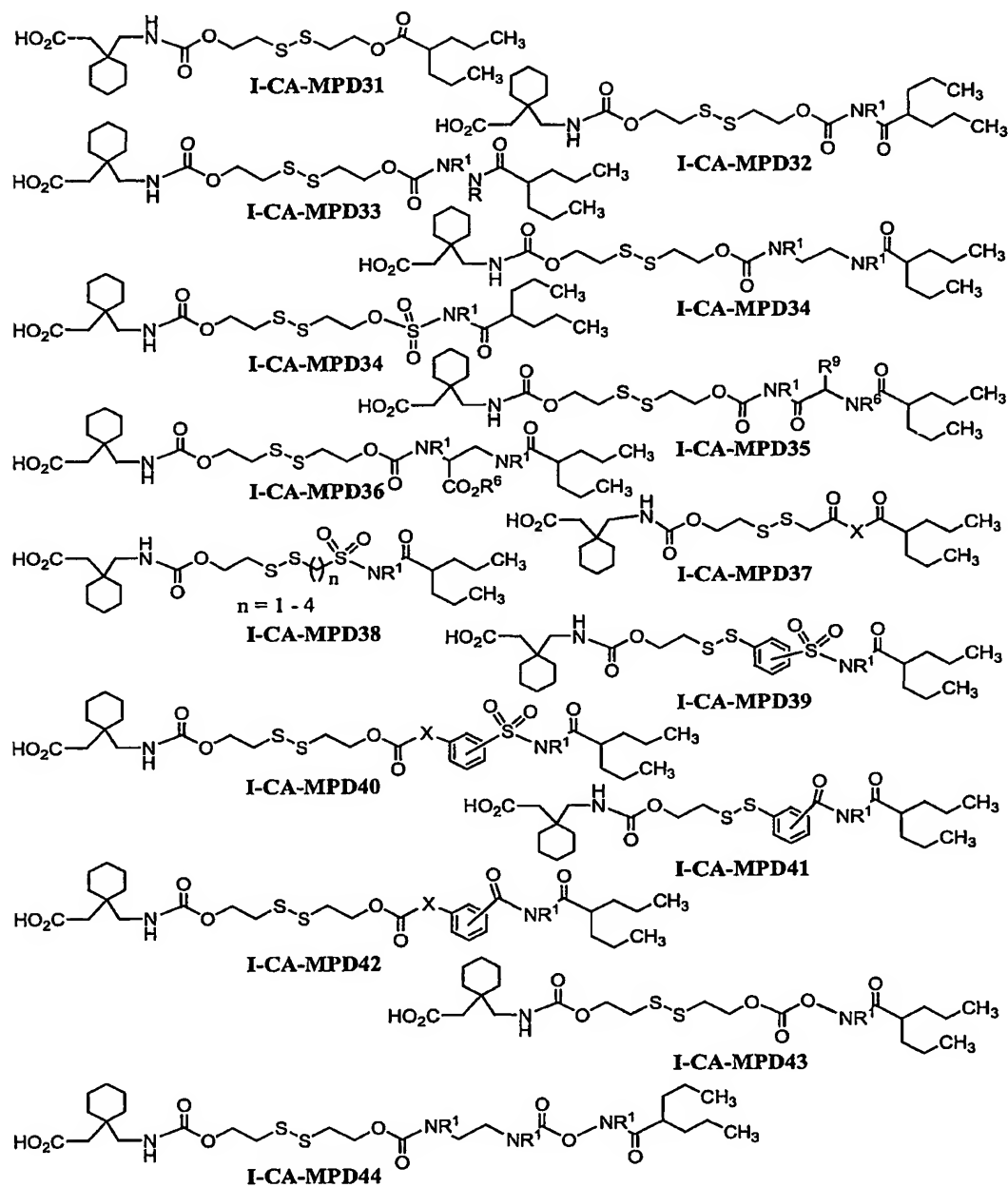
10



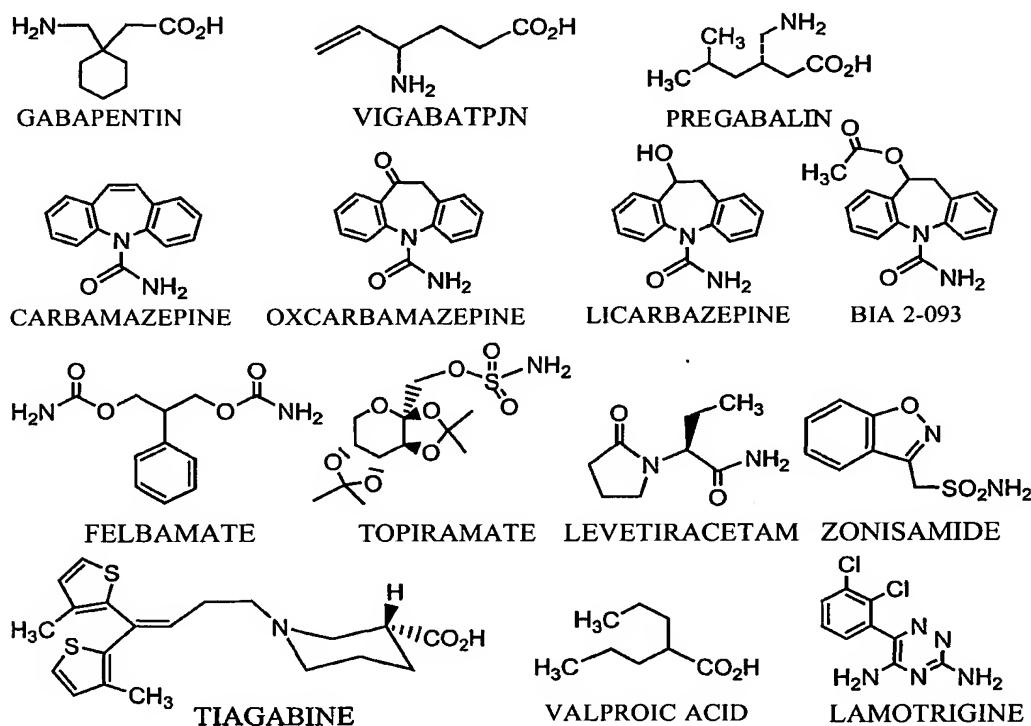
Mutual prodrugs made from an amino-containing therapeutic agent and a carboxyl-containing therapeutic agent:

15 A mutual prodrug of cetirizine and pseudoephedrine (I-CA-MPD1) is proposed for treatment of rhinitis. Cetirizine is an antihistamine and pseudoephedrine is a nasal decongestant.

Mutual prodrugs of gabapentin and valproic acid are potential antiepileptic agents. This same kind of prodrug may be a potential treatment option for patients with
20 bipolar disorder and other mental illnesses. The following are some of the examples:



Other illustrative examples of mutual prodrugs under this category include the following: Mutual prodrugs of valproic acid and other carboxyl-, hydroxyl-, and amino-containing (including amide-, and sulfonamide-containing) anticonvulsant agents such as levetiracetam, lamotrigine, pregabalin, carbamazepine, oxcarbazepine, licarbazepine, felbamate, topiramate and the like. (Structures are given below). The list also includes investigational antiepileptic agents such as antipamezole, licarbazepine, Eslicarbazepine Acetate (BIA 2-093), fluorofelbamate, isovaleramide (NPS 1776), retigabine (D-23129), safnamide (NW-IOI 5), stiripentol (STP), talampanel (TLP), (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide 83alpha (ucb 34714), valroceamide (TV 1901), and the like.



Mutual Prodrugs can be made from combination of any two anti-convulsant agents listed above or any other suitable anticonvulsant agents.

Mutual prodrug of gabapentin and naproxen (I-CA-MPD22) is proposed for potential treatment option for neurological pain and inflammation.

Mutual prodrugs made from an amino-containing therapeutic agent and a hydroxyl-containing therapeutic agent:

Mutual prodrugs of norfloxacin and metronidazole (I-AH-MPD1, I-AH-MPD2, I-AH-MPD3) are proposed for potential treatment of diarrhea and dysentery of bacterial, amoebic and mixed origin. Metronidazole is an antianaerobic agent and used in combination with antibiotics such as norfloxacin, ciprofloxacin, etc. for the treatment of patients with diarrhea and dysentery of bacterial, amoebic and mixed origin.

A mutual prodrug of loperamide and norfloxacin (I-AH-MPD4) is proposed for potential treatment of diarrhea and dysentery.

10 A mutual prodrug of valdecoxib and tramadol (I-AH-MPD5 and I-AH-MPD6) as a potential therapy in postoperative pain management.

A mutual prodrug of gabapentin and tramadol (I-AH-MPD7) is proposed for potential treatment of neuropathic pain after spinal cord injury.

15 A mutual prodrug of venlafaxine and paroxetine (I-AH-MPD8) is proposed for potential treatment of neurological and depression related disorders.

Mutual prodrugs made from a hydroxyl-containing therapeutic agent and another hydroxyl-containing therapeutic agent:

20 Mutual prodrugs of zidovudine (AZT/Retrovir) and lamivudine (3TC/Epivir) (I-HH-MPD1, I-HH-MPD2) are proposed as a potential treatment option for HIV and other viral infections.

POTENTIAL EXAMPLES OF WATER-SOLUBLE PRODRUGS:

Water-soluble prodrugs of insoluble/sparingly-soluble therapeutic agents can be prepared using the same linker technology.

25 Water-soluble prodrugs of metronidazole include: I-H1-PD-2, I-H1-PD-3, I-H1-PD-4.

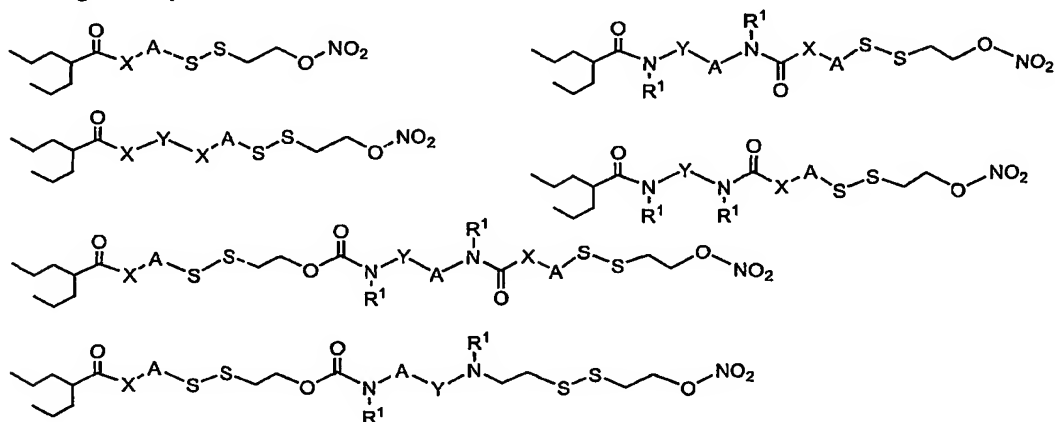
Water-soluble prodrugs of valdecoxib include: I-A3-PD1, I-A3-PD2a, I-A3-PD2b, I-A3-PD3a, I-A3-PD3b, I-A3-PD4, I-A3-PD5, I-A3-PD6, and I-A3-PD7b.

Water-soluble prodrugs of paclitaxel include: I-Taxol-PD1, I-Taxol-PD2, I-Taxol-PD3, I-Taxol-PD4, I-Taxol-PD5, I-Taxol-PD6, and I-S23-PD1.

30 **POTENTIAL EXAMPLES OF NO-RELEASING PRODRUGS:**

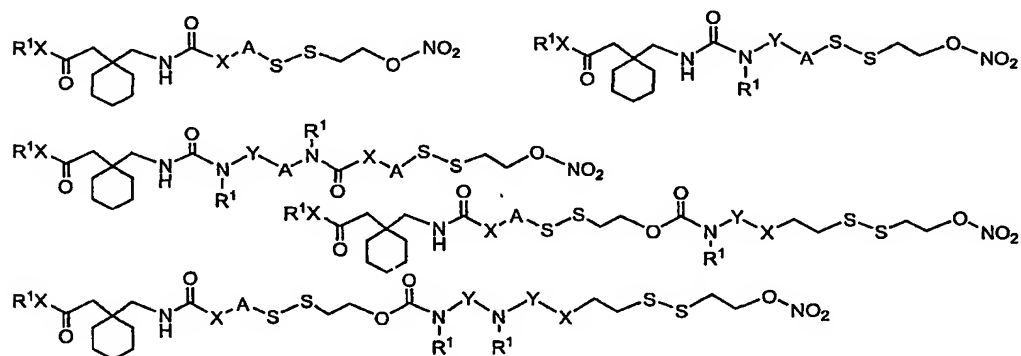
In the following potential examples, X is O, NR¹ (R¹ = H, alkyl) or a bond; Y is CO, SO₂, PC=O)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or (CH₂)₀ (° = 0-6) and m is 1-2 unless otherwise stated;

Prodrugs of Valproic Acid (Anticonvulsant):

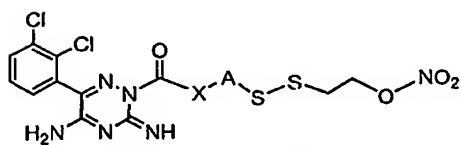


5

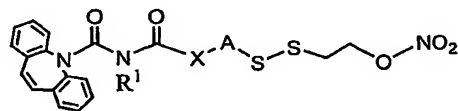
DRUGS CONTAINING REACTIVE PRIMARY AND SECONDARY AMINES, AMIDE-NH, UREA-NH, SULFONAMIDE-NH, SULFAMATE-NH, AND CARBAMATE-NH:



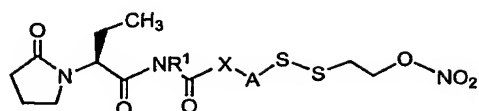
Prodrugs of Gabapentin (Anticonvulsant):



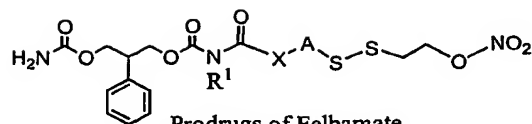
Prodrugs of Lamotrigine
(Anticonvulsant):



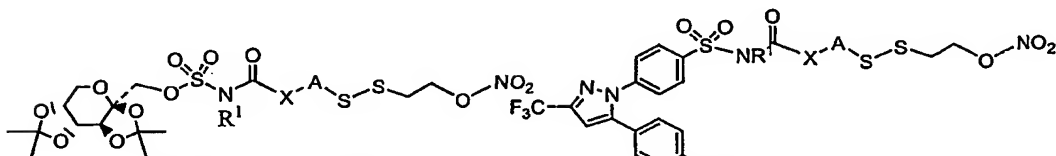
Prodrugs of Carbamazepine
(Anticonvulsant):



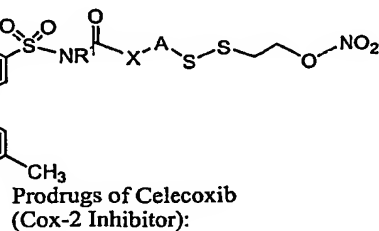
Prodrugs of Levetiracetam
(Anticonvulsant):



Prodrugs of Felbamate
(Anticonvulsant):

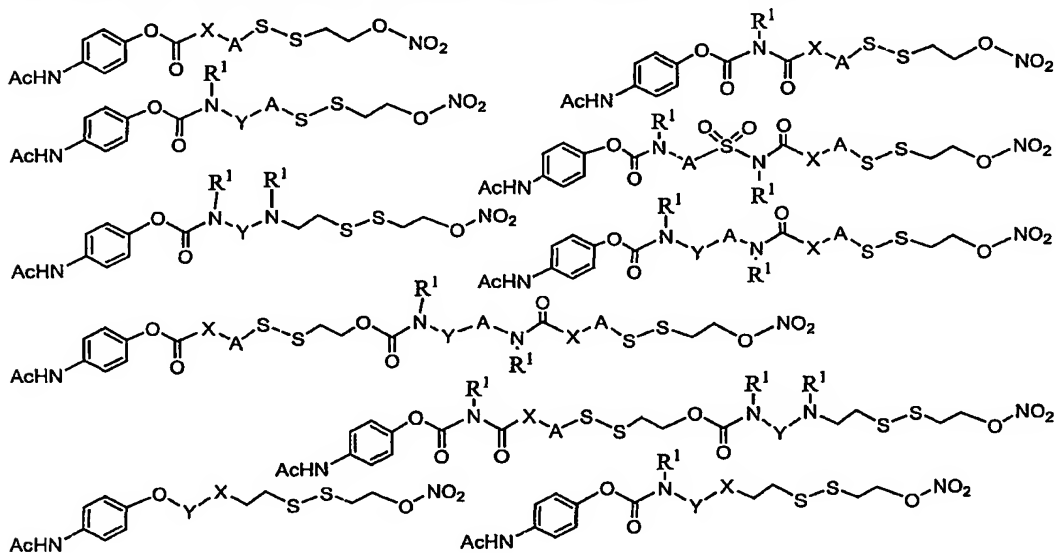


Prodrugs of Topiramate
(Anticonvulsant):



Prodrugs of Celecoxib
(Cox-2 Inhibitor):

NO-Releasing Prodrugs of Paracetamol/Acetaminophen (Analgesic and Antipyretic):



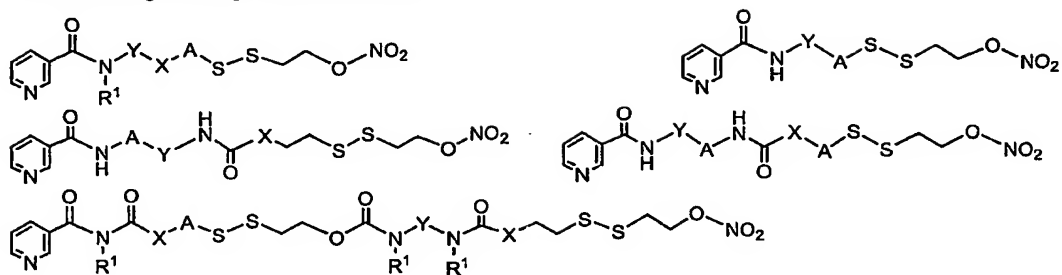
5

ADDITIONAL POTENTIAL EXAMPLES:

In the following additional potential examples, X is O, NR¹ (R¹ = H, alkyl) or a bond; Y is CO, SO₂, PC=O)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or (CH₂)₀ (o = 0-6) and m is 1-2 unless otherwise stated;

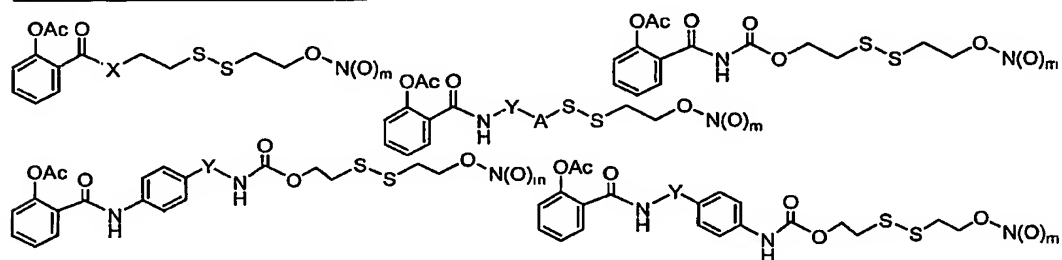
10

NO-Releasing Prodrugs of Nicotinamide:

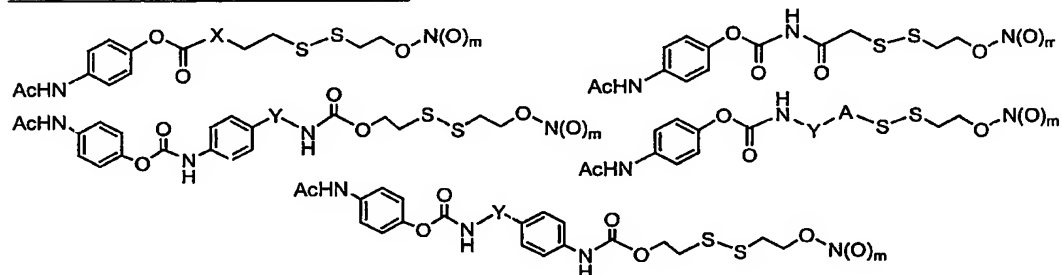


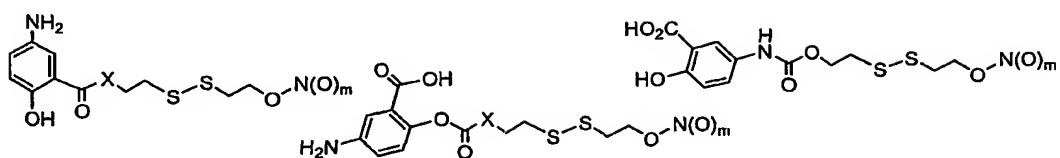
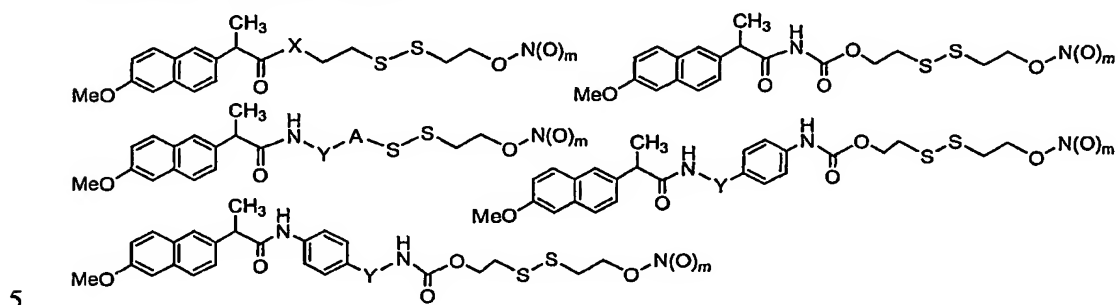
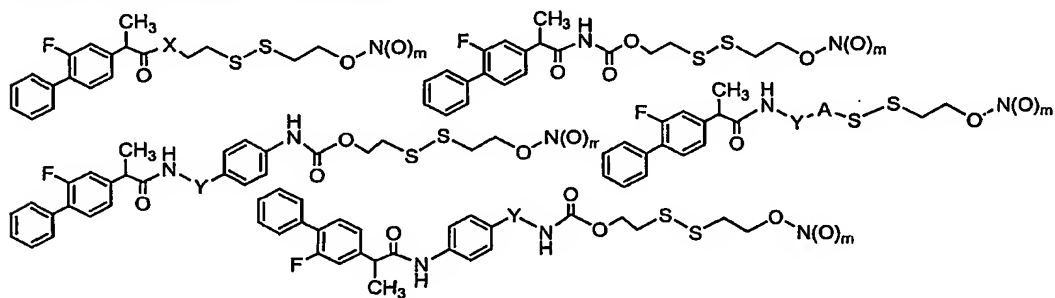
NO-Releasing Prodrugs of NSAIDs:

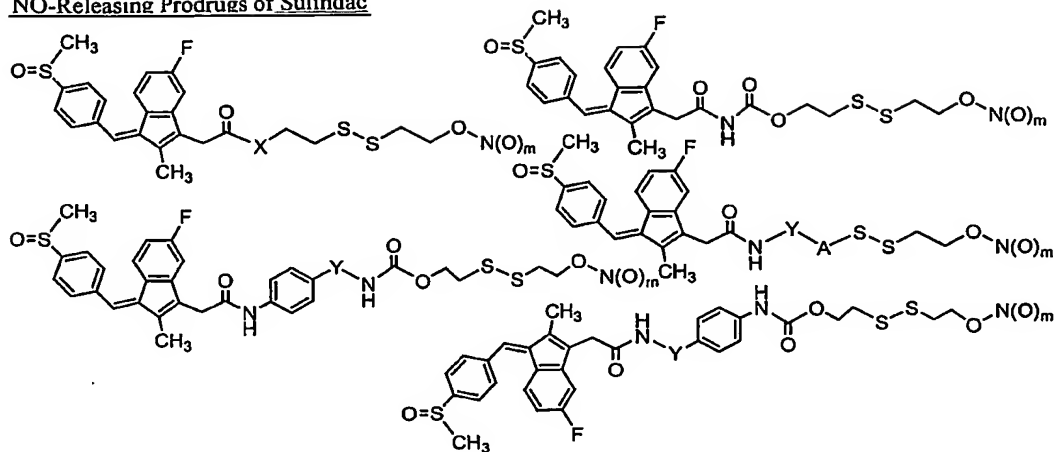
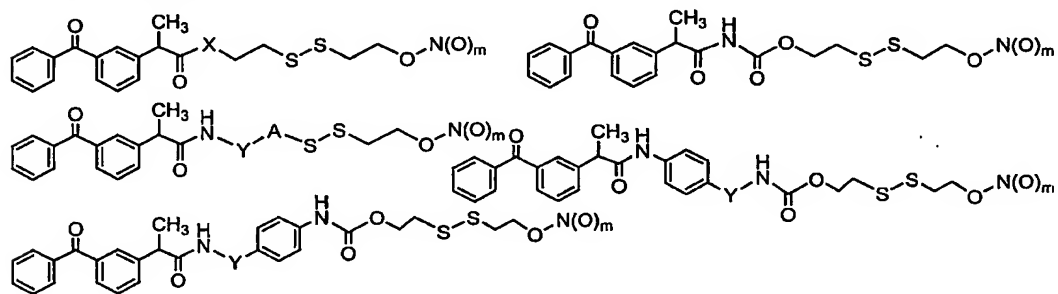
NO-Releasing Prodrugs of Aspirin

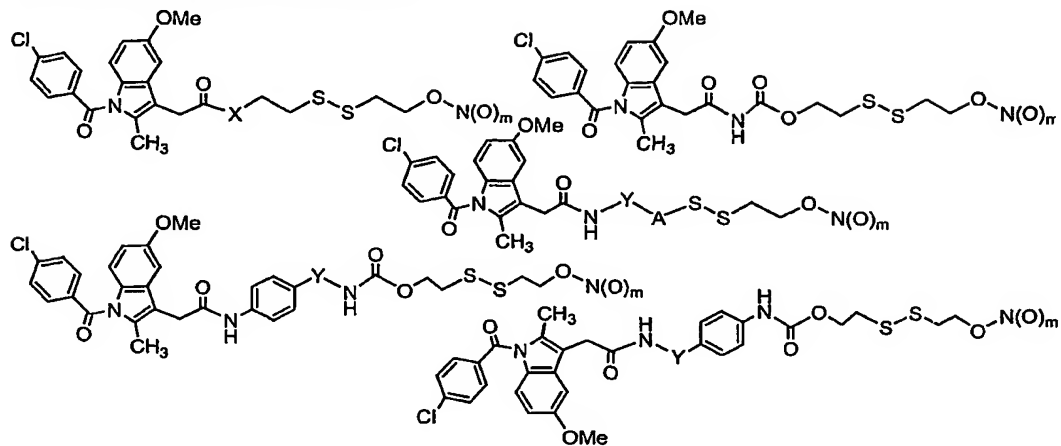
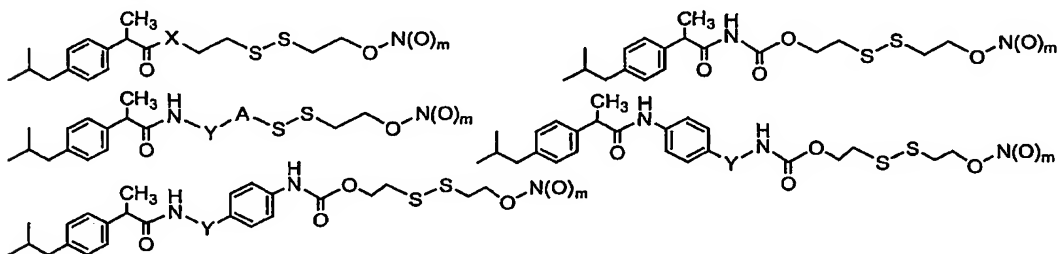
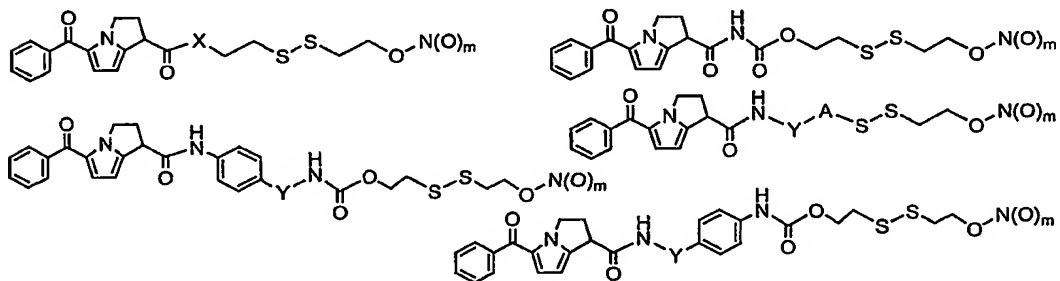


NO-Releasing Prodrugs of Paracetamol

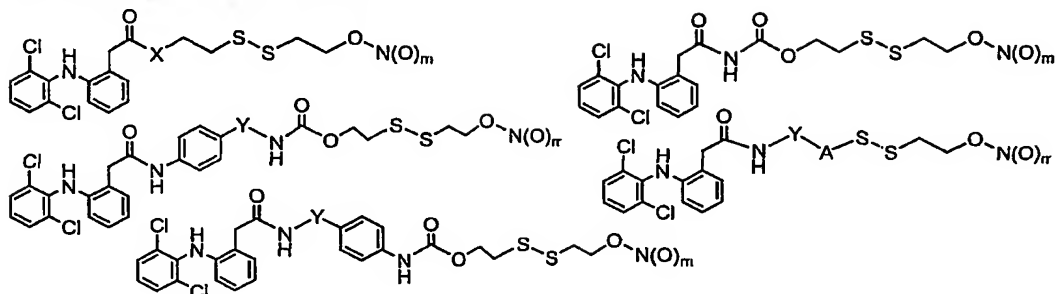


NO-Releasing Prodrugs of MesalamineNO-Releasing Prodrugs of NaproxenNO-Releasing Prodrugs of Flurbiprofen

NO-Releasing Prodrugs of SulindacNO-Releasing Prodrugs of Ketoprofen

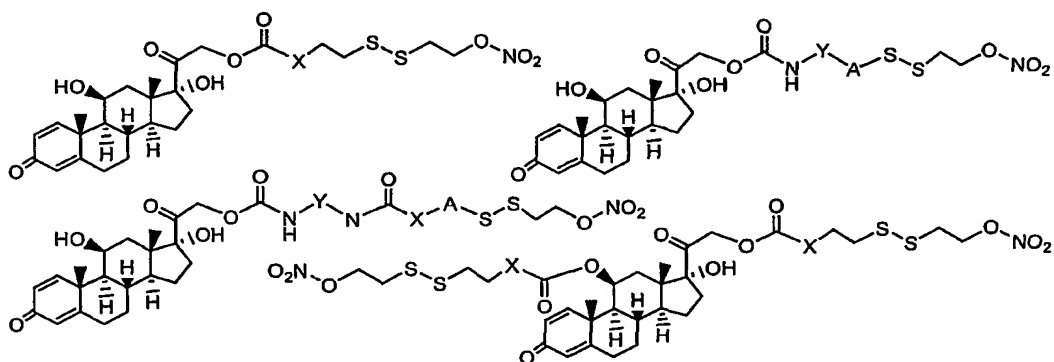
NO-Releasing Prodrugs of IndomethacinNO-Releasing Prodrugs of IbuprofenNO-Releasing Prodrugs of Ketorolac

NO-Releasing Prodrugs of Diclofenac

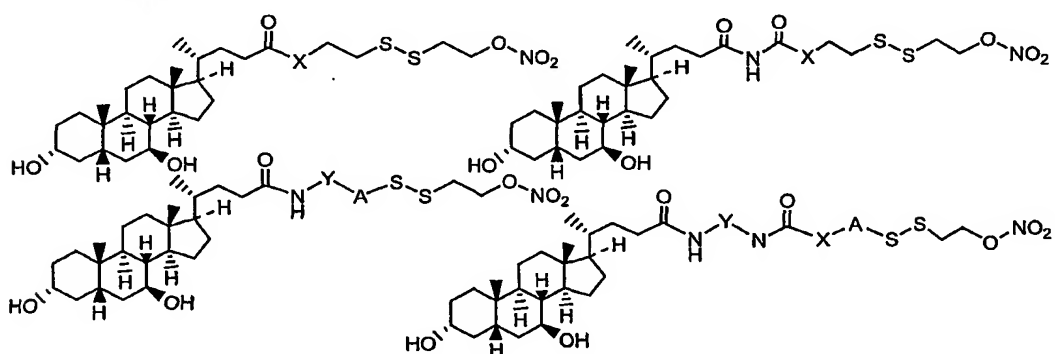


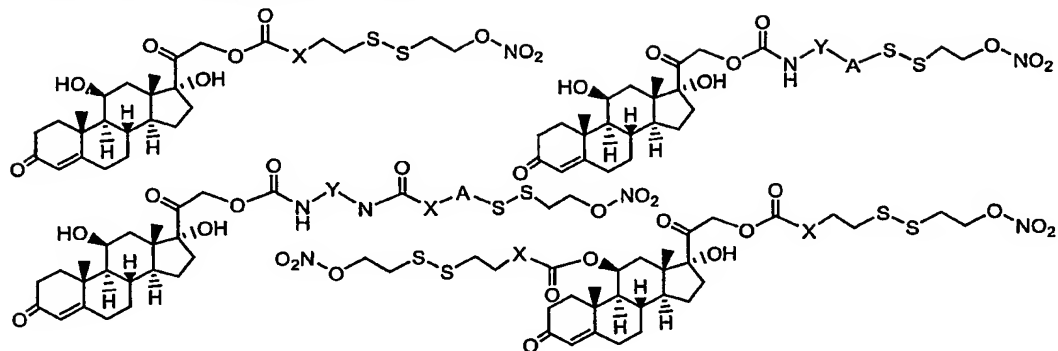
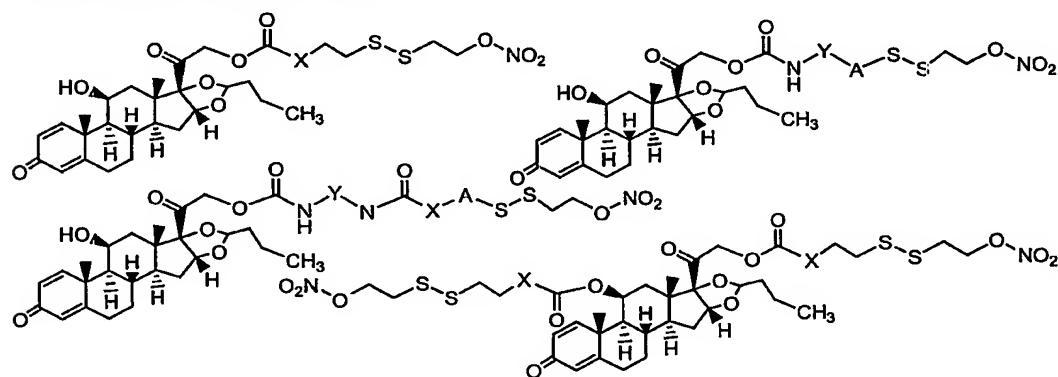
NO-Releasing Prodrugs of Glucocorticoids:

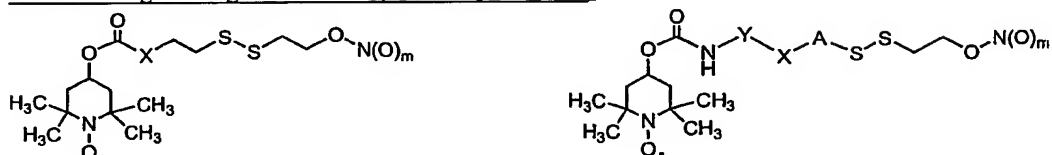
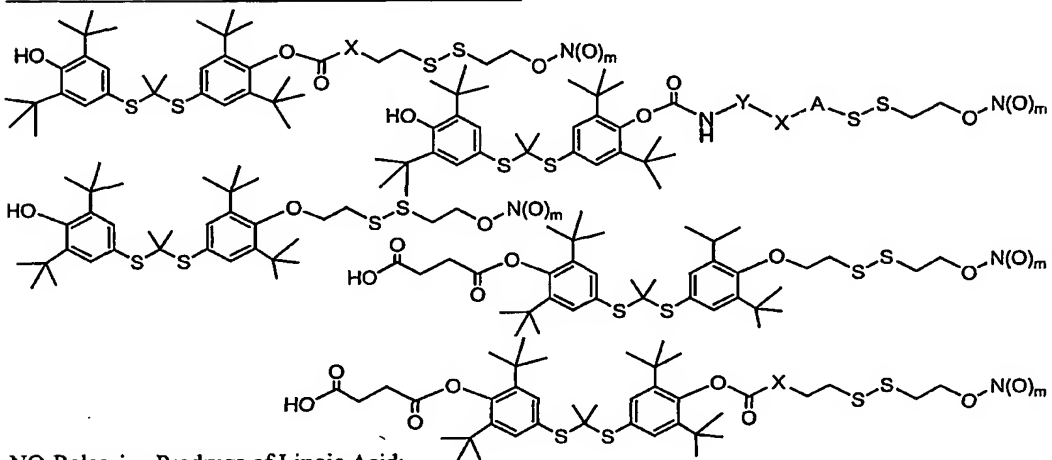
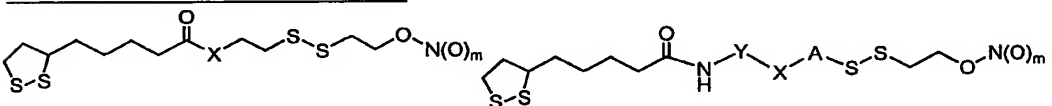
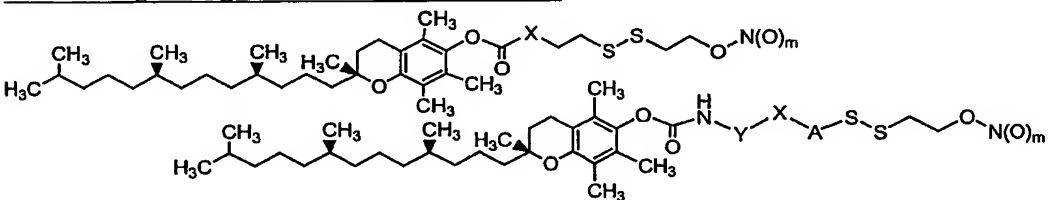
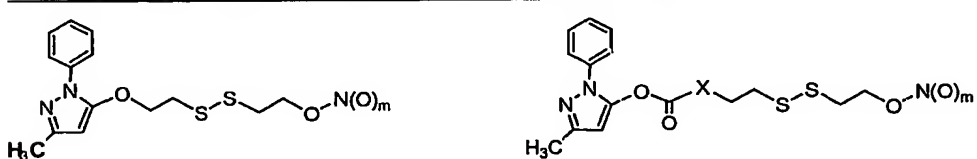
NO-Releasing Prodrug of Prednisolone

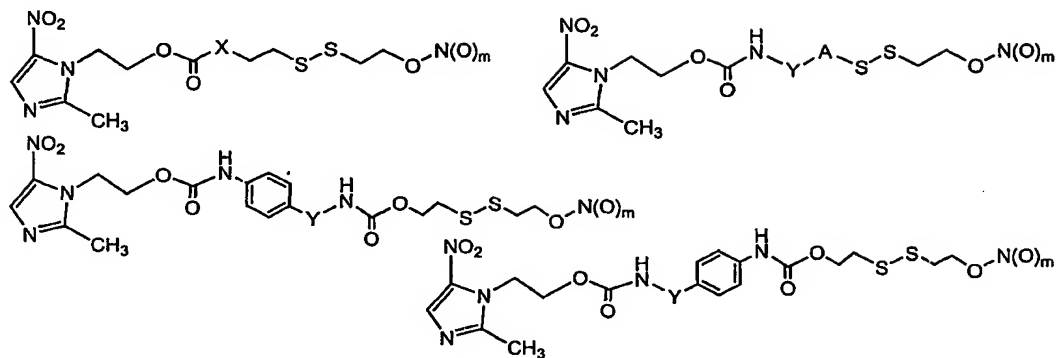
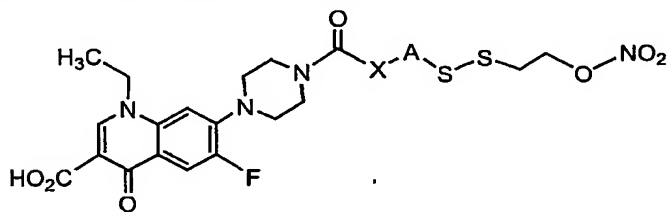
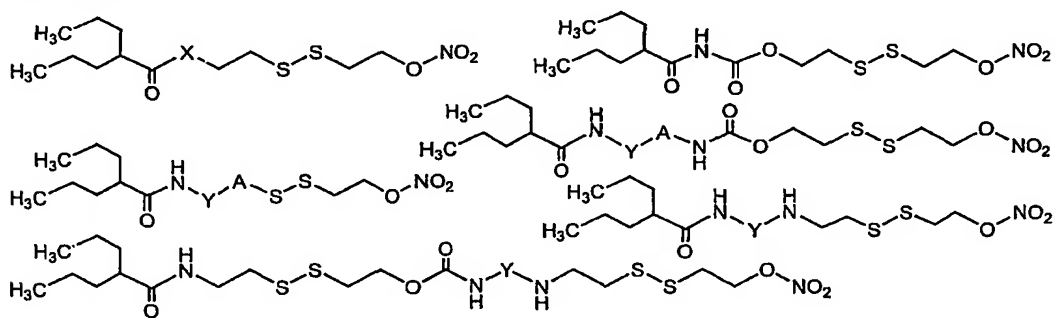


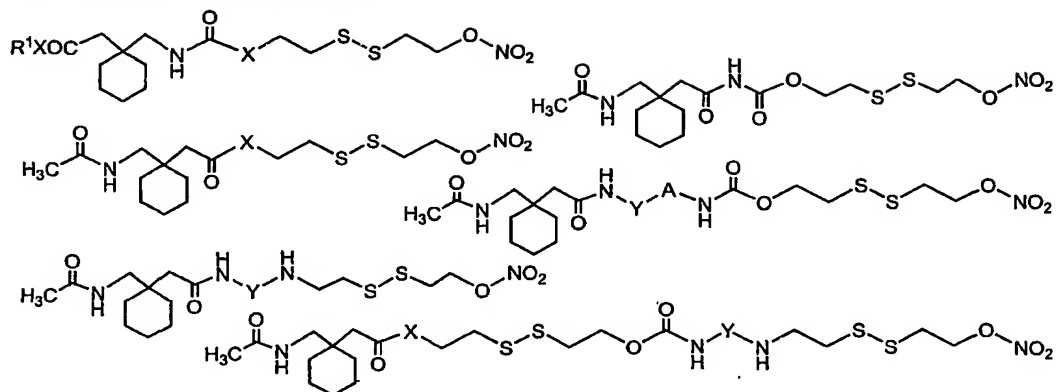
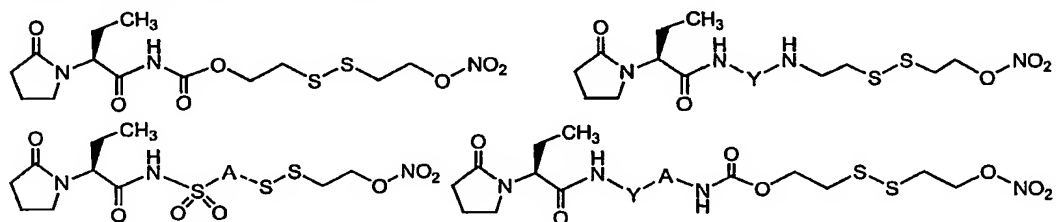
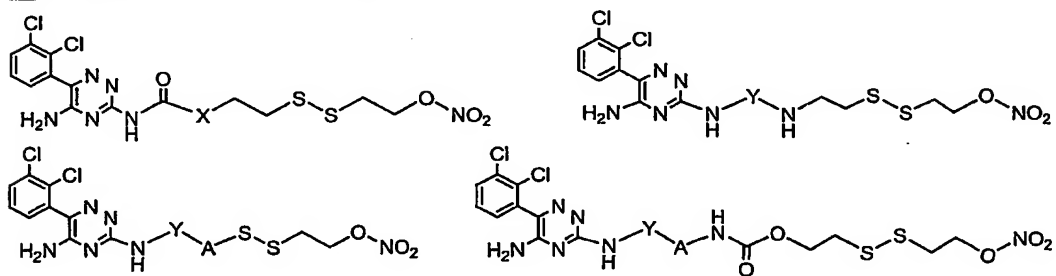
NO-Releasing Prodrug of Ursodeoxycholic Acid

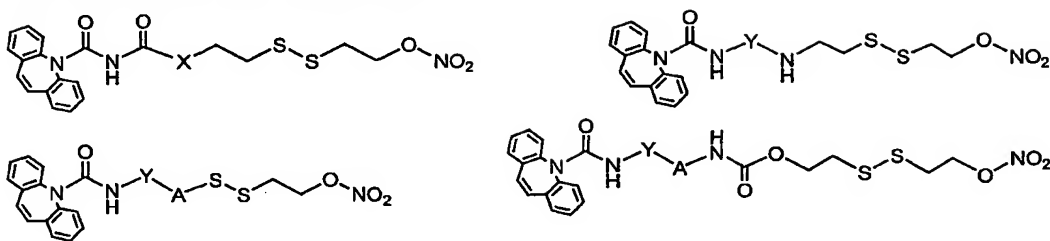


NO-Releasing Prodrug of HydrocortisoneNO-Releasing Prodrug of Budesonide

NO-Releasing Prodrugs of Antioxidants and /or Free Radical Scavengers:NO-Releasing Prodrug of TEMPOL (4-hydroxy-TEMPO):NO-Releasing Prodrugs of Probucol and AGI-1067:NO-Releasing Prodrugs of Lipoic Acid:NO-Releasing Prodrugs of Vitamin E (alfa-tocopheroD:NO-Releasing Prodrugs of Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one):

NO-Releasing Prodrugs of Antibiotics:NO-Releasing Prodrugs of MetronidazoleNO-Releasing Prodrugs of Norfloxacin:**NO-Releasing Prodrugs of Antiepileptic Agents:**NO-Releasing Prodrugs of Valproic Acid

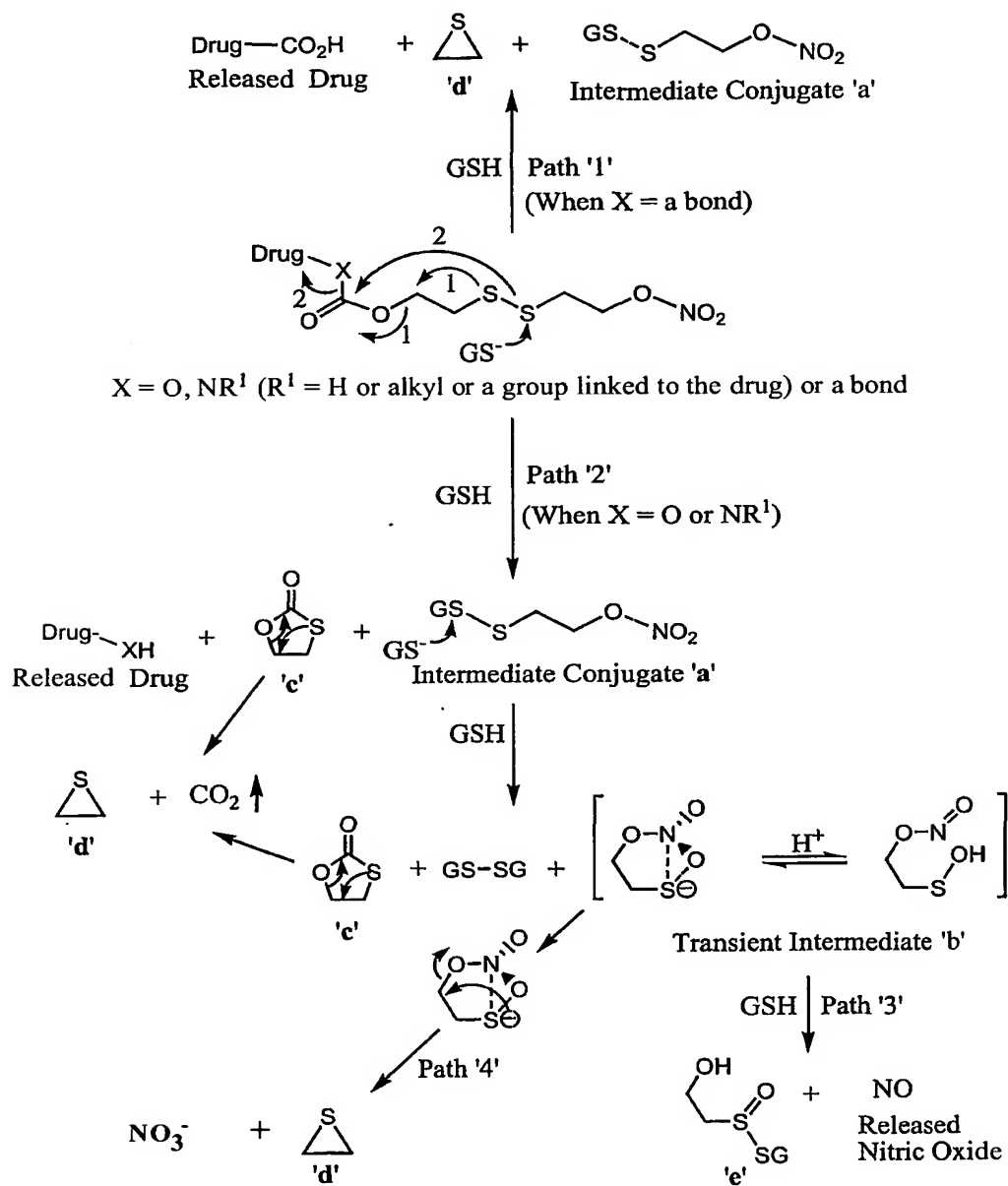
NO-Releasing Prodrug of GabapentinNO-Releasing Prodrug of LevetiracetamNO-Releasing Prodrug of Lamotrigine

NO-Releasing Prodrug of Carbamazepine5 Plausible Mechanisms of Drug Release from Prodrugs

Drugs can be released from the prodrugs and mutual prodrugs via cleavage of bio-labile linker(s) in vivo (cleavage can be either chemical or enzymatic or both) by illustrative mechanisms as shown in Schemes M1 through M5.

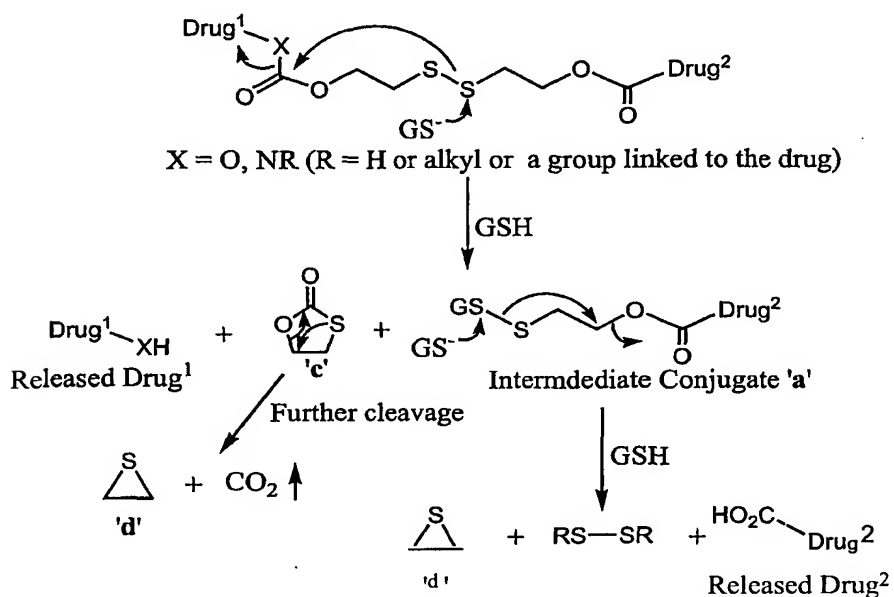
Plausible mechanisms for concomitant release of nitric oxide (NO) and free drug from NO-releasing prodrug(s) of amino-, hydroxyl-, or carboxyl-containing drug(s) are illustratively shown in Schemes M1. Thus, the attack of thiolate ion (from GSH or any other sulfahydryl-containing species) on nitrooxy-containing prodrug would release carboxylic acid-containing free drug, episulfide (d) and the intermediate conjugate (a) according to path 1. If the prodrugs are made from amino-, or hydroxyl-containing drugs, then the prodrug would be cleaved via path 2 to release the corresponding free drug, the cyclic thiocarbonate intermediate (c) and the intermediate conjugate (a). The cyclic thiocarbonate intermediate may further breakdown into episulfide (d) and carbon dioxide. The reactive episulfide (d) would be further neutralized by glutathione. The nitrate ester-containing intermediate conjugate can further break down in the presence of GSH to glutathione dimer (GS-SG) and transient intermediate (b), which can break down via path

3 to release NO. It is also possible the same transient intermediate can break down via path 4 to yield episulfide (d) and a relatively innocuous nitrate anion (NO_3^-).



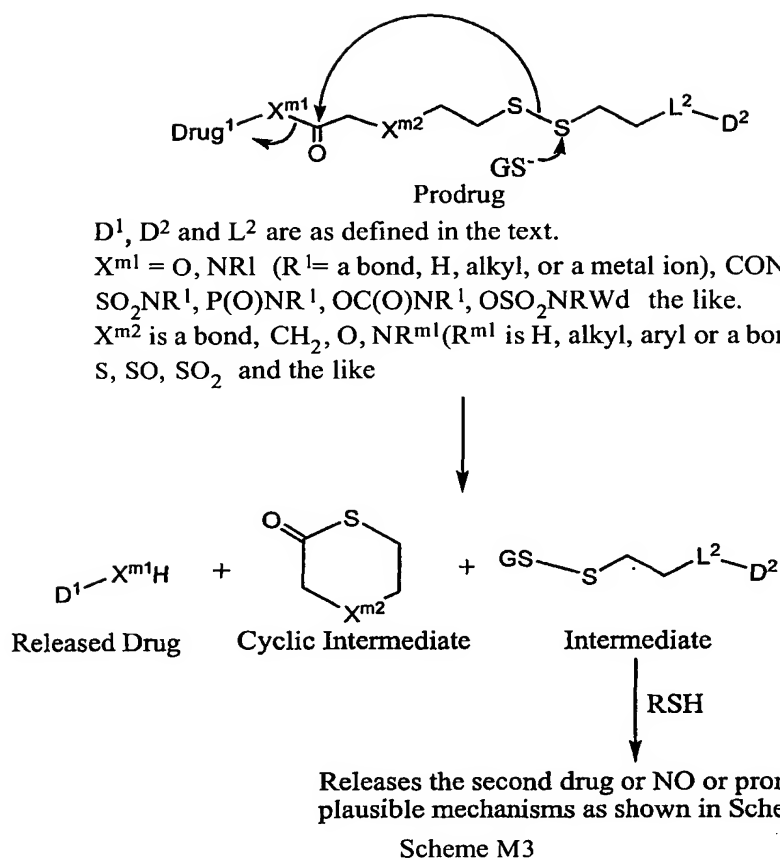
Scheme M1

Plausible mechanisms of drug release from mutual prodrugs of one carboxyl-containing and one amino-/hydroxyl-containing drug is shown in Scheme M2.



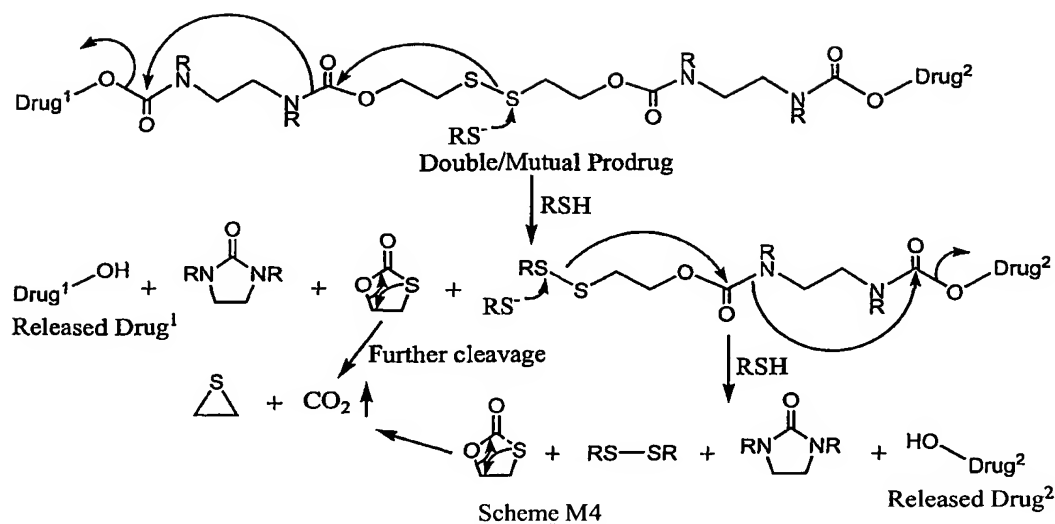
Scheme M2

Plausible mechanism of drug release from prodrugs (including mutual and NO-releasing prodrugs of amino-, hydroxyl- and carboxyl-containing drugs) containing modified bio-labile linkers is shown in Scheme M3. Thus, the thiolate anion derived from the attack of glutathione on disulfide of the prodrug may trigger cyclization to release the free drug (DI-X^mH) and a stable six-membered (or five-membered, if Xⁿ is a bond) thio-lactone intermediate.

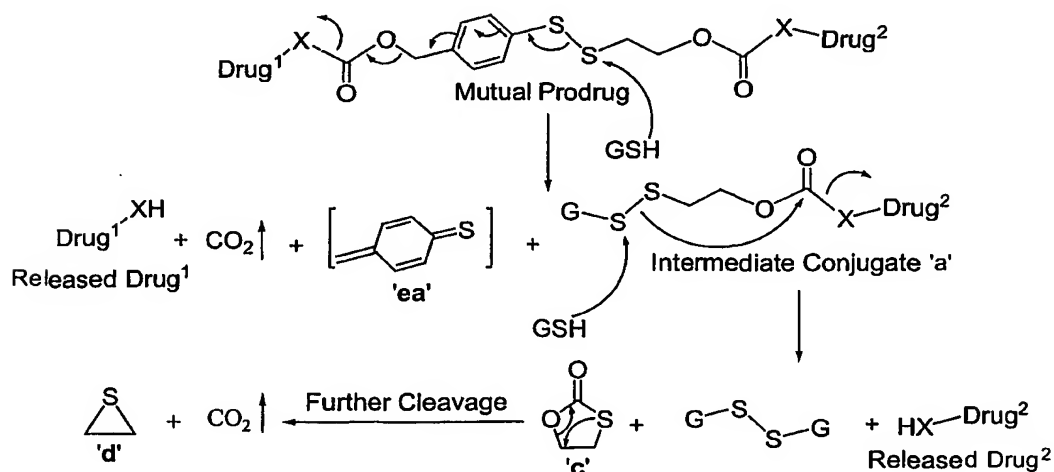


Plausible mechanisms of drug release from double/mutual prodrugs containing additional linkages to couple two hydroxyl-containing drugs are shown in Scheme M4.

- 5 Thus, the thiolate anion generated by the attack of glutathione on disulfide bond of the prodrug triggers further cleavage as shown to release the free drug (D^1-OH) and a five-membered 2-imidazolidone. Through in vitro decomposition studies, we have found that the drug release from this type of prodrug is more facile when R group is an alkyl group.

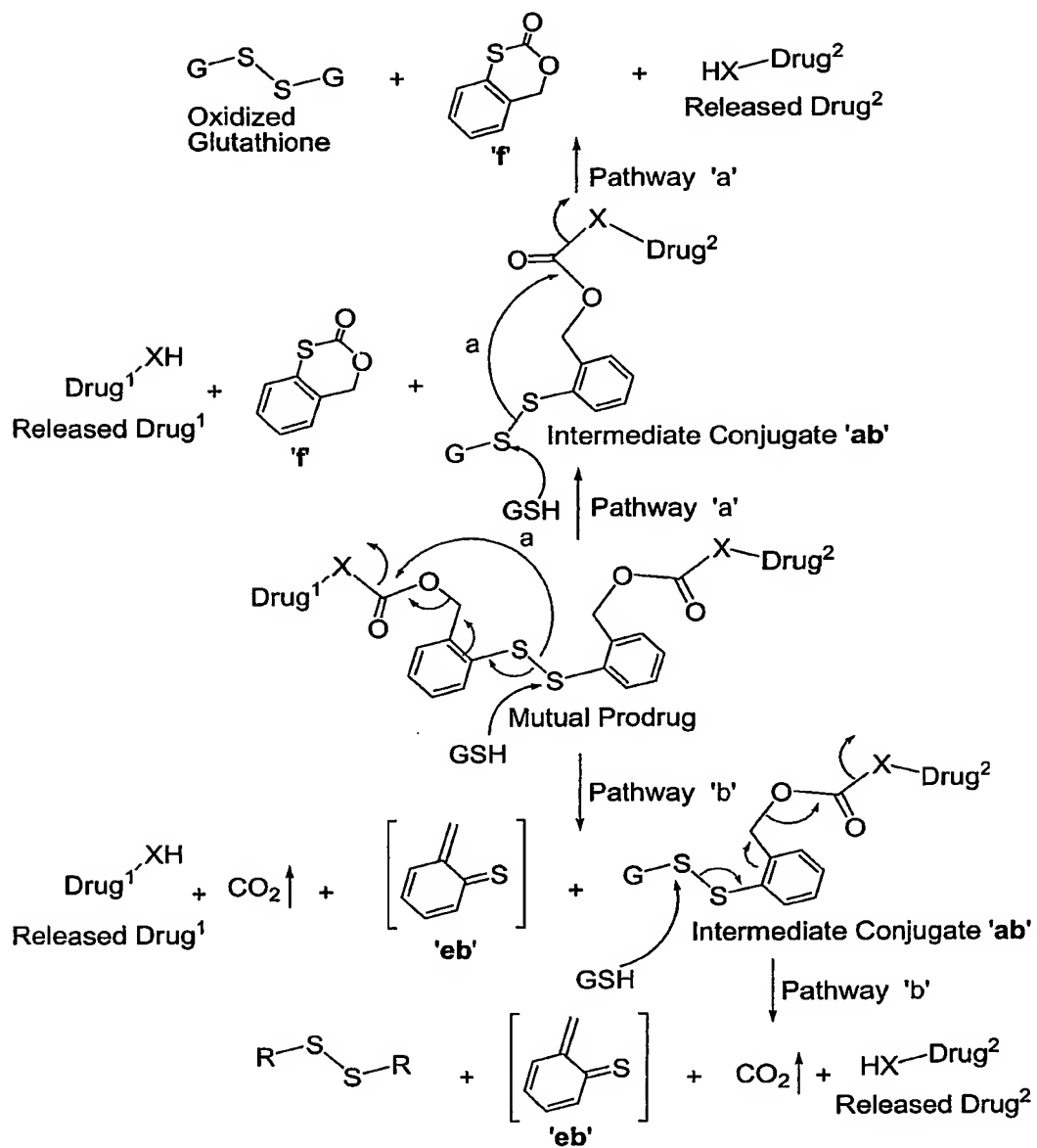


This invention also covers novel bio-labile linkers containing 1,4-phenylene group and 1,2-phenylene group as shown in Schemes 5 and 6, respectively. As depicted in Scheme M5, the linker is expected to release the free Drug¹ upon glutathione-assisted cleavage and may generate 1,4-quinonemethid (ea) as a byproduct via 1,6-elimination process. Similarly, the free Drug² is expected to be released from the intermediate conjugate (a) as shown in the scheme.



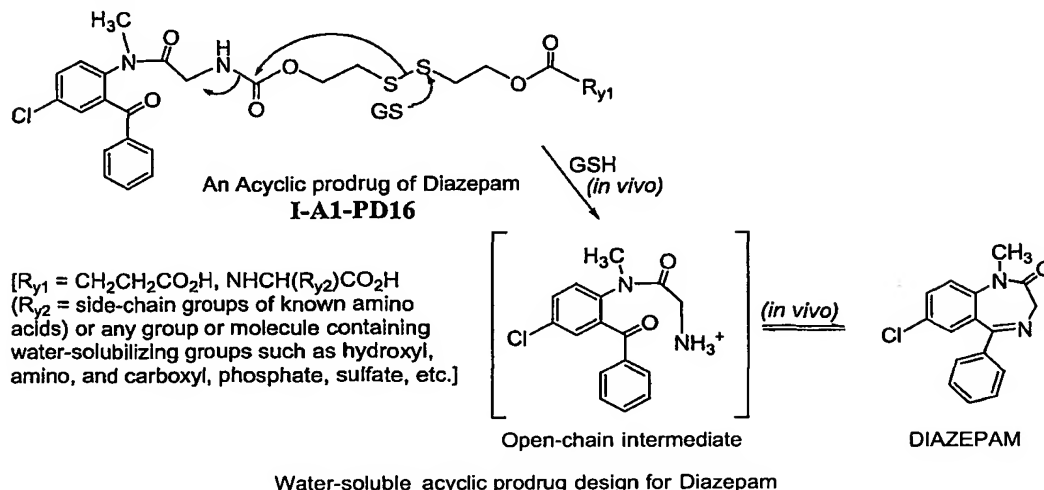
As depicted in Scheme M6, the 1,2-phenylene-containing linker is also expected to release free drugs upon glutathione assisted cleavage and generate 1,2-quinonemethide (eb) as a byproduct via 1,4-elimination process (via pathway 'b'). However, this linker can also cleave via pathway 'a' to generate benzo-monothiocarbonate as a byproduct.

- 5 Although the generated byproducts seem to be toxic, they are likely to be quickly neutralized by detoxification enzymes in the body.



Scheme M6

Scheme M7: Plausible mechanism of diazepam formation from an acyclic prodrug of diazepam



Diazepam, a benzodiazepine tranquilizer, is very sparingly water-soluble drug and a water-soluble acyclic prodrug of diazepam can be made by using our linker technology.

- 5 As shown in the Scheme M7, reduction of disulfide bond in the prodrug triggers release of open-chain intermediate of diazepam which spontaneously cyclizes to diazepam *in vivo*.

- Where GSH is glutathione (reduced) or any other *in vivo* bioreductive agent that can reduce the disulfide bond. As illustrated, cleavage of disulfide bond triggers further
- 10 breakage of the remaining portion of the linker to release the free drugs. In the process, some byproducts are generated and these are either eliminated or further degraded by some biological process. For clarity, the mechanism of cleavage of the linker is shown as occurring in stepwise manner. However, both the steps can possibly occur in a concomitant fashion to release both the drugs simultaneously.

- 15 As illustrated in Scheme M3 and M4, Linkers may have additional spacer groups between one side (or both sides) of the linkers and the drug molecule and some of these spacer groups may be cleaved independently by a chemical or enzymatic process to release the drugs prematurely before the cleavage of disulfide linkage. The prodrugs and mutual prodrugs containing such spacer groups may be useful when faster release of
- 20 drug(s) is desired.

LISTS OF CANDIDATE DRUGS USEFUL FOR PRODRUG SYNTHESIS:

Drugs listed in the following list can be converted to NO- releasing prodrugs. This list is in no way limiting the scope of drugs covered in this invention, but given as representative examples. All the amino- (including amide-NH and sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH, urea-NH, phosphoramidate-NH and the like. See above, for the description of "amino-containing drugs"), carboxyl-, hydroxyl-(including oxime-OH), and carbonyl (both aldehyde and keto groups)-containing drugs under various therapeutic categories as listed in Merck Index (13th editions) and other data bases such as Pubmed, Science's ensemble, integrity, and the like and also all the qualified (i.e., amino-, and /or hydroxyl-, and/or carboxyl-, and/or carbonyl-containing) investigational drugs as listed in databases such as Merck Index (13th editions), Pubmed, ensemble, integrity, and the like, are covered under this invention without any limitation.

ANTI-INFLAMMATORY DRUGS:

Amino-containing (including Amide NH and Sulphonamide NH and Phosphonamide NH, etc.): Ampiroxicam, Bucolome, Celecoxib, Difenpiramide, Mofebutazone, Nimesulide, Paranyline, Parecoxib, Parsalmide, Piketopufen, Talniflumate, Tenidap, Terofenamate, and Valdecoxib.

Hydroxyl-containing: 21-Acetoxyprogesterone, Alclometasone, alfa-Bisabolol, Budesonide, Deflazacort, Diflorasone, Desonide, Desoximetasone, Diflorasone, Diflucortolone, Difenprednate, Ditalol, Fluazacort, Fluocinonide, Fluocortin Butyl, Fluprednidene Acetate, Glucametasin, Halcinonide, Halobetasol Propionate, Halometasone, Halopredone Acetate, Ibuprofen, Loteprednol Etabonate, Maziapredone, Mometasone Furoate, Oxyphenbutazone, Perisoxal, Rimexolone,

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphonamide NH, etc.): Bufexamac, Etofenamate, Fepradinol, Ibuprofen, Isoxicam, Lornoxicam, Meloxicam, Oxametacine, Piroxicam, and Tenoxicam.

Hydroxyl- and sulphahydryl-containing: Tixocortol,

Carboxyl- and Amino-containing (including amide NH and sulfonamide NH and phosphonamide NH, etc.): Aceclofenac, Alminoprofen, Amfenac, 3-Amino-4-

hydroxybutyric Acid, Carprofen, Diclofenac, Enfenamic Acid, Etodolac, Flufenamic Acid, Meclofenamic Acid, Mefenamic Acid, Niflumic Acid, and Tolfenamic Acid.

Carboxyl-containing: Acemetacin, Acetamidocaproic Acid, Bendazac, Benoxaprofen, Betnoprofen, Bucloxic Acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Felbinac, Fenbufen, Fenclozic Acid, Fenoprofen, Fentiazac, Flunoxaprofen, Flurbiprofen, Ibuprofen, Indomethacin, Isofezolac, Isoxepac, Ketoprofen, Lonazolac, Loxoprofen, Metiazinic Acid, Mofezolac, Naproxen, Oxaprozin, Pirazolac, Pirprofen, Pranoprofen, Protizinic Acid, Sulindac, Suprofen, Suxibuzone, Tiaprofenic Acid, Tolmetin, and Tropesin.

Carboxyl- and Hydroxyl-containing: Balsalazide, Enoxolone, Fendosal, Olsalazine, Oxaceprol, and Ximoprofen.

Amino-, Carboxyl- and Hydroxyl-containing: 3-Amino-4-hydroxybutyric Acid, Mesalamine, and Sulfasalazine.

Keto-containing: Nabumetone, and Piketoprofen.

Carboxyl- and keto-containing: Bermoprofen, Bucloxic Acid, Isoxepac, Ketoprofen, Loxoprofen, and Zaltoprofen.

ANALGESIC AND/OR ANTIPYRETIC DRUGS:

Amino-containing: Aminochlorthenoxazin, Aminopropylon, Anileridine, Antrafenine, Benorylate, Benzpiperylon, p-Bromoacetanilide, Butacetin, Carsalam, Difenamizole, Etersalate, Ethenzamide, Ethoxazene, Flipirtine, Isonixin, Nifenazone, Phenacetin, Phenazopyridine, Phenocoll, Phenopyrazone, Piminodine, Piritramide, Propacetamol, Ramifenazone, Piperylone, Salverine, and Tinoridine.

Hydroxyl-containing: Aluminum bis(acetylsalicylate), Benzylmorphine, Buprenorphine, Butorphanol, Chlorobutanol, Ciramadol, Codeine, Desomorphine, Dihydrocodeine, Dihydromorphine, Dihydroxyaluminum acetylsalicylate, Dimepheptanol, Eptazocine, Ethylmorphine, Eugenol, Hydroxypethidine, Levorphanol, Meptazinol, Metazocine, Morphine, Nalbuphine, Pentazocine, Phenazocine, Phenoperidine, Phenylsalicylate, Salicin, Tramadol, and Viminol.

Carboxyl-containing: Acetylsalicylic acid, Alclofenac, Aspirin, Benoxaprofen, 5-Bromosalicylic acid acetate, Cinchophen, Diacerein, Dipyrrocetyl, Fosfosal, Ibufenac, Indoprofen, and Salicysulfuric acid.

Amino- and Hydroxyl-containing: Acetaminophen, Acetaminosalol, Bucetin, Capsaicine, Dezocine, Floctafenine, Glafenine, Isoladol, p-Lactophenetide, Norlevorphanol, Norphenorphine, Phenylramidol, Salacetamide, and Salicylamide.

Amino- and Carboxyl-containing: Actarit, Bumadizone, Clonixin, and
5 Salicylamide O-acetic acid.

Carboxyl- and Hydroxyl-containing: Diflunisal, Gentisic acid, and Salsalate.

Keto-containing: Amtolmetin, Dipipanone, Hydrocodone, Isomethadone, Methadone, Norpipanone, and Phenadoxone.

Hydroxy- and Keto-containing: Hydromorphone, Ketobemidone, Metopon,
10 Oxycodone, and Oxymorphone.

Carboxyl- and Keto-containing: Clometacin, Ketorolac, and Zomepirac.

Amino- Carboxyl- and Keto-containing: Bromfenac.

ANTIHYPERTENSIVE DRUGS:

Amino-containing: Alfuzosin, Benzylhydrochlorothiazide, Bethanidine,
15 Bopindolol, Budralazine, Bunazosin, Ciclosidomine, Clonidine, Clopamide, Cyclopenthiazide, Debrisoquin, Edesofidine, Diazoxide, Dihydralazine, Doxazosin, Endralazine, Guanabenz, Guanacine, Guanazodine, Guanethidine, Guanochlor, Guanadrel, Guanfacine, Guanoxan, Hydracarbazine, Hydralazine, Hydroflumethiazide, Indapamide, Indoramin, Irbesartan, Ketanserin, Lofexidine, Mebutamate,
20 Mecamylamine, Methyl 4-primidyl ketone thiosemicarbazone, Mibefradil, Minoxidil, Monatepil, Moxonidine, Pheniprazine, Pinacidil, Prazosin, Raubasine, Rescinnamine, Reserpiline, Reserpine, Rilmenidine, Syrosingopine, Tasosartan, Terazosin, Tiamenidine, Todralazine, Tolonidine, Tripamide, and Urapidil.

Hydroxy-containing: Ajmaline, Cicletanine, Levromakalim, Naftopidil,
25 Phenactropinium chloride, and Protoveratrine.

Carboxyl-containing: Eprosartan, Fosinopril, and Telmisartan,

Amino- and Carboxyl-containing: Alacepril, gamma-Aminobutyric acid, Benazepril, Candesartan, Carmoxirole, Caronapril, Cilazapril, Delapril, Enalapril, Enalaprilat, Imidapril, Lisinopril, Moexipril, Moveltipril, Perindopril, Quinapril,
30 Ramipril, Saralasin, Spirapril, Temocapril, Trandolapril, and Valsartan.

Amino- and Hydroxyl-containing: Acebutolol, Alprenolol, Amosulalol, Arotinolol, Atenolol, Betaxolol, Bisoprolol, Bosentan, Bucindolol, Bufeniode, Bunitrolol, Bupranolol, Butofilolol, Cadralazine, Celiprolol, Carazolol, Carteolol, Cetamolol, Carvedilol, Epanolol, Indenolol, Nadolol, Dilevalol, Fenoldopam, Guanoxabenz, 5 Labetalol, Losartan, Mepindolol, Metipranolol, Metoprolol, Moprolol, Nebivolol, Olmesartan, Oxprenolol, Penbutolol, Phentolamine, Pildralazine, Pindolol, Propranolol, Rescimetol, Sulfinalol, Talinolol, Tertatolol, Timolol, and Trimazosin.

Amino-, Hydroxyl- and Carboxyl-containing: Methyldopa, and Sampatrilat, Sulfahydryl- and Carboxyl-containing: Captopril, and Omapatrilat, 10 Carbonyl-containing: Aranidipine, and Eplerenone, ANTIBIOTICS:

All the known amino-, hydroxyl-, and carboxyl-containing antibiotics such as Amoxicillin, Ampicillin, Olivanic acid, Metronidazole, and the like as listed in Merck Index. 13th edition and other drug databases integrity, ensemble, iddb, and the like. These 15 antibiotics can be used in combination with beta-lactamase inhibitor such as clavulanic acid, penicillinic acid sulfone and the like. The following lists of antibacterial and antifungal agents are given for clarity.

ANTIBACTERIAL AGENTS:

Amino-containing: Acedapsone, Acetosulfone sodium, Ambazone, Bacampicillin, 20 Benzylsulfamide, Brodimoprim, Cefcapene pivoxil, Cefpodoxime proxetil, Chloramine-B, Chloramine-T, Capreomycin, Clofazimine, Cyacetamide, Cycloserine, Dapsone, Ethionamide, Furazolidine, N2-Formylsulfinisomidine, Furazolidine, Isoniazid, Lenampicillin, Linezolid, Mafenide, 4'-(Methylsulfonyl)sulfanilamide, Morphazinamide, Nifuradene, Nitrofurantoin, Penamocillin, Penethamate hydriodide, 25 Pexiganan, Pivampicillin, Pivcefalexin, Picloxydine, Protionamide, Pyrazinamide, Solasulfone, Subathizone, 4,4'-Sulfinyldianiline, Sulfoxone sodium, 4'-Sulfanilylsulfanilamide, Sulfoniazide, Sulfabenzamide, Sulfacetamide, Sulfachlorpyridazine, Sulfacycline, Sulfadiazine, Sulfadiazine, Sulfadimethoxine, Sulfadoxine, Sulfathiazole, Sulfaguanidine, Sulfaguanole, Sulfalene, Sulfamerazine, 30 Sulfameter, Sulfamethazine, Sulfamethazole, Sulfamethomidine, Sulfamethoxazole, Sulfamethoxypyridazine, Sulfamethylthiazole, Sulfametrole, Sulfamidochrysoidine,

Sulfamoxole, Sulfanilamide, p-Sulfanilylbenzylamine, Sulfanilylurea, N-Sulfanilyl 1-3,4-xylamide, Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfasomizole, Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfisomidine, Sulfisoxazole, Sultamicillin, Sulfatolamide, Talampicillin, Taurolidine, Tetroxoprim, Thiazosulfone, Thiacetazone, 5 Tiocarlide, and Trimethoprim.

Hydroxyl-containing: Azithromycin, Chloroxylenol, Chlorquinadol, Clofoctol, Cloxyquin, Diathymosulfone, Glucosulfone sodium, Nifurpirinol, Nifurtinol, Nitroxoline, Roxarsone, Roxithromycin, Xanthocillin, and Xibornol.

Carboxyl-containing (including sulfate, phosphate and phosphonate-containing):
10 Amdinocillin, Cinoxacin, Difloxacin, Fosfomycin, and Hydnocarpic acid.

Amino- and Carboxyl-containing (including sulfate-, sulfonic acid-, phosphate and phosphonate-containing): Acediasulfone, Amphomycin, Ampicillin, Azidocillin, Azlocillin, Aztreonam, Bacitracin, Balofloxacin, Betamipron, Carbenicillin, Carindacillin, Carumonam, Cefaclor, Cefazedone, Cefazolin, Cefclidin, Cefditoren, 15 Cefepime, Cefetamet, Cefixime, Cefmenoxime, Cefmetazole, Cefodizime, Ceforanide, Cefotaxime, Cefotetan, Cefotiam, Cefoxitin, Cefozopran, Cefpimizole, Cefpirome, Cefroxadine, Cefsulodin, Ceftazidime, Cefteram, Ceftezole, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Cefuzonam, Cephacetrile sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalosporin C, Cephalothin, Cephapirin sodium, Cephradine, 20 Cilastatin, Ciproflaxacin, Clinafloxacin, Clometocillin, Cyclacillin, Dicloxacillin, Enoxacin, Epicillin, Fenbenicillin, Floxacillin, Hetacillin, Loracarbef, Metampicillin, Methicillin, Mezlocillin, Nafcillin, Noprysulfamide, Opiniastide, Oxacillin, Penicillin(s), Penimepicycline, Phenethicillin, Phthalylsulfacetamide, Phthalylsulfathiazole, Piperacillin, Propicillin, Quinacillin, Succinylsulfathiazole, Succisulfone, Sulbenicillin, 25 Sulfachrysoidine, Sulfanilic acid, Temocillin, Ticarcillin, and Tigemonam.

Amino- and Hydroxyl-containing: Amikacin, p-Aminosalicylic acid hydrazide, Arbekacin, Azidamfenicol, Bambermycins, 5-Bromosalicylhydroxamic acid, Butirosin, Clindamycin, Clomocycline, Chloramphenicol, Cloxacillin, Colistin, Demeclocycline, Deoxydihydrostreptomycin, Dibekacin, Dihydrostreptomycin, Dirithromycin, 30 Doxycycline, Enviomycin, Ethambutol, Forimicins, Gentamycin, Glyconiazide, N4-beta-D-Glucosylsulfanilamide, Gramicidin(s), Isepamicin, Kanamycin(s), Lincomycin,

Meclocycline, Methacycline, Micronomicin, Neomycin, Netilmicin, Novobiocin, Paromomycin, Phenyl aminosalicylate, Pipacycline, Polymyxin, Primycin, Ramoplanin, Ribostamycin, Rifabutin, Rifalazil, Rifamide, Rifamycin SV, Rifampin, Rifapentine, Rifaximin, Ristocetin, Salinazid, Sancycline, Sisomicin, Streptolydigin, Streptomycin, 5 Streptonicozid, 2-p-Sulfanilylanilinoethanol, Thiamphenicol, Thiostrepton, Tobramycin, Tuberactinomycin, Viomycin, and Virginiamycin.

Hydroxyl- and Carboxyl-containing (including sulfate, phosphate and phosphonate-containing): Fropenem, Nadifloxacin, Biapenem, Fusidic acid, and Merbromin.

10 Hydroxyl- and Aldehyde-containing: Josamycin, Leucomycins, Midecamycins, Miokamycin, Rokitamycin, and Spiramycin.

Amino-, Hydroxyl-, and Carboxyl-containing (including sulfate, phosphate and phosphonate-containing): p-Aminosalicylic acid, Apicycline, Amoxicillin, Apalcillin, Aspoxicillin, Benzoylpas, Cefadroxil, Cefamandole, Cefatrizine, Cefbuperazone, 15 Cefdinir, Cefminox, Cefonicid, Cefoperazone, Cefoselis, Cefpiramide, Cefprozil, Ertapenem, Flomoxef, Imipenem, Lymecline, Meropenem, Moxalactam, Negamycin, Panipenem, Ritipenem, Salazosulfadimidine, Sulfaloxic acid, 4-Sulfanilamidosalicylic acid, Teicoplanin, Tyrocidine, and Vancomycin.

Keto-containing: Troleandomycin.

20 Hydroxy- and Keto-containing: Carbomycin, Clarithromycin, Erythromycin, all erythromycin ester derivatives, Oleandomycin, and Telithromycin.

Hydroxy-, Aldehyde-, and Keto-containing: Rosaramicin.

Amino- and Keto-containing: Porfiromycin.

Carboxyl- and Keto-containing: Fleroxacin, Flumequine, Miloxacin, Nalidixic acid, Ofloxacin, Oxolinic acid, Pefloxacin, Piromidic acid, Prulifloxacin, Rosoxacin, and 25 Rufloxacin.

Amino-, hydroxyl-, and Keto-containing: Chlortetracycline, Dalfopristin, Guamecycline, Mikamycin, Minocycline, Oxytetracycline, Pristinamycin, Quinupristin, Rolitetracycline, Spectinomycin, and Trospectomycin.

Amino-, carboxyl-, and keto-containing: Garenoxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Pazufloxacin, Pipemidic acid, Sitafoxacin, Sparfloxacin, Tosufloxacin, and Trovafloxacin.

Sulfahydryl-containing: Pyrithione.

5 ANTIFUNGAL AGENTS:

Amino-containing: Chlordantoin, Exalamide, Flucytosine, Loflucarban, Magenta I, and Pyrrolnitrin.

Hydroxy-containing: Chlophenesin, Ciclopirox, Dermostatin, Filipin, Fluconazole, Fungichromin, Pecilocin, Posaconazole, Ravuconazole, Rubijervine,
10 Siccanin, 2,4,6-Tribromo-m-cresol and Voriconazole.

Carboxyl-containing: Undecylenic acid (10-undecenoic acid), and Propionic acid,

Amino- and Carboxyl-containing: Azaserine.

Amino- and Hydroxyl-containing: Salicylanilide, Acrisorcin (9-Aminoacridine
15 compound with 4-Hexylresorcinol (1:1)), Anidulafungin, Bromosalicylchloranilide, Buclosamide, Caspofungin, Micafungin, and Tubercidin.

Amino-, Carboxyl- and Hydroxyl-containing: Natamycin, Amphotericin B, Lucensomycin, and Nystatin.

Carbonyl-containing: sodium propionate and griseofulvin.

20 Hydroxy- and carbonyl-containing: Viridin.

Amino-, hydroxyl-, and carbonyl-containing: Perimycin and Mepartricin.

Amino-, carboxyl-, hydroxyl-, and carbonyl-containing: Candicidin.

ANTIVIRAL DRUGS:

Hydroxy-containing: Edoxudine, Floxuridine, Idoxuridine, Kethoxal,
25 Podophyllotoxin, Sorivudine, Stavudine, Trifluridine, and Zidovudine.

Amino-containing: Amantadine, Amidinomycin, Atevirdine, Capravirine, Delavirdine, Efavirenz, Famciclovir, Imiquimod, Lamivudine, Methisazone, Moroxydine, Nevirapine, Oseltamivir, Rimantadine, Stallimycin, mantadine, and Valacyclovir.

30 Amino- and Hydroxyl-containing: Abacavir, Acyclovir, Adefovir, Amprenavir, Atazanavir, Cidofovir, Didanosine, Dideoxyadenosine, Emtricitabine, Entecavir,

Indinavir, Lamivudine, Lopinavir, 5-(methylamino)-2-deoxyuridine (MADU), Nelfinavir, Penciclovir, Resiquimod, Ribavirin, Ritonavir, Saquinavir, Tenofovir, Tipranavir, Valganciclovir, Vidarabine, and Zalcitabine.

Carboxyl- and Hydroxyl-containing: Foscarnet sodium, and Ganciclovir.

5 Amino-, Carboxyl- and Hydroxyl-containing: Zanamivir.

ANTIMALARIAL:

Amino-containing: Chlorguanide, Chloroquine, Chlorproguanil, Cycloguanil, Pamaquine, Plasmocid, Primaquine, Quinocide, and Tafenoquine.

Hydroxyl-containing: Artemisinin alcohol, Bebeerines, Cinchonidine,
10 Cinchonine, Dihydroartemisinin, Halofantrine, Lumefantrine, Quinine and Yingzhaosu A.

Carboxyl-containing: Arteflene and Artesunate.

Amino-, and Hydroxyl-containing: Amodiaquin, Hydroxychloroquine, Mefloquine, and Pyronaridine.

15 Hydroxyl, and carbonyl-containing: Fosmidomycin.

Carbonyl-containing: Arteflene.

ANTINEOPLASTIC DRUGS:

Hydroxy-containing: Aclacinomycins, Arzoxifene, Batimastat, Broxuridine, Calusterone, Capecitabine, CC-1065, Chromomycins, Diethylstilbestrol, Docetaxel,
20 Doxifluridine, Droloxifene, Dromostanolone, Enocitabine, Eptiostanol, Estramustine, Etanidazole, Etoposide, Fenretinide, Flavopiridol, Formestane, Fosfestrol, Fulvestrant, Gemcitabine, Irinotecan, Melengestrol, Menogaril, Miltefosine, Mitobronitol, Mitolactol, Mopidamol, Nitracrine, Nogalamycin, Nordihydroguaiaretic Acid, Olivomycins, Paclitaxel and other known paclitaxel analogs, Plicamycin, Podophyllotoxin, Retinoic
25 acid (including all trans-retinoic acid), Roquinimex, Rubitecan, Seocalcitol, Temoporfin, Teniposide, Tenuazonic Acid, Topotecan, Valrubicin, Vinblastine, Vincristine, and Zosuquidar.

Amino-containing (including Amide-NH and Sulphonamide-NH, Carbamate-NH, Sulfamate-NH, and Phosphomide-NH): 9-Aminocamptothecin, Aminolevulinic Acid,
30 Amsacrine, Bisantrone, Cactinomycin, Carboquone, Carmofur, Carmustine, Cyclophosphamide, Dacarbazine, Dactinomycin, Demecolcine, Diaziquone, 6-Diazo-5-

oxo-L-norleucine (DON), Edatrexate, Efaproxiral, Eflornithine, Eniluracil, Erlotinib, Fluorouracil, Gefitinib, Gemcitabine, Goserelin, Histamine, Ifosfamide, Imatinib, Improsulfan, Lanreotide, Leuprolide, Liarozole, Lobaplatin, Cisplatin, Carboplatin, Lomustine, Lonafernib, Mannomustine, Melphalan, Methotrexate, Methyl
 5 Aminolevulinate, Miboplatin, Mitoguazone, Mitoxantrone, Nilutamide, Nimustine, Nolatrexed, Oxaliplatin, Pemetrexed, Phenamet, Piritrexim, Procarbazine, Raltitrexed, Tariquidar, Temozolomide, Thiamiprine, Thioguanine, Tipifarnib, Tirapazamine, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP)/ 3-Aminopyridine-4-methyl-2-carboxaldehyde thiosemicarbazone (3-AMP/Triapine /OCX-191/OCX-0191),
 10 Trimetrexate, Uracil Mustard, Uredepa ([Bis(l-aziridinyl)phosphinyl]carbamic acid ethyl ester, ethyl carbamate and Meturedapa.

Both Hydroxy- & Amino- containing (including Amide-NH and Sulphonamide-NH, Carbamate-NH, Sulfamate-NH, and Phosphomide-NH): Ancitabine, Anthramycin, Azacitidine, Bleomycins, Bropiramine, Buserelin, Carubicin, Chlorozotocin, Cladribine,
 15 Cytarabine, Daunorubicin, Decitabine, Defosfamide, Docetaxel, Doxorubicin, Ecteinascidins, Epirubicin, Gemcitabine, Hydroxyurea, Idarubicin, Marimastat, 6-Mercaptopurine, Pentostatin, Peplomycin, Perfosfamide, Pirarubicin, Prinomastat, Puromycin, Ranimustine, Streptonigrin, Streptozocin, Tiazofurin, Troxacitabine, Vindesine and Zorubicin.

20 Carboxyl-containing: Butyric acid.

ANTIOXIDANTS/FREE RADICAL SCAVENGERS:

Amino-containing (including some investigational drugs): BTX-51072 (4,4-dimethyl-3,4-dihydro-2H-1,2-benzoselenazine), Carnosine, Melatonin, (+)-R-Pramipexole, and Stobadine.

25 Hydroxyl-containing (including some investigational drugs): Ascorbic acid, Curcumin, Dexanabinol, Edaravon, (-) Epigallocatechin Gallate, Emoxipin, Hydroxytyrosol, Idebenone, Luteolin, Nicanartine, NZ-419, Oxyresveratrol, Probucol (including probucol prodrugs such as AGI-1067 and AGI-1096), Quercetin, Reductic acid, Silybin, Tempol (4-Hydroxy-TEMPO), and alfa-Tocopherol (Vitamin E).

30 Carboxyl-containing (including some investigational drugs): N-Acetyl L-cysteine, Alfa-Lipoic acid, Raxofelast, and Tetomilast.

Amino-/Hydroxyl-, and Carboxyl-containing (including some investigational drugs): N-Acetyl carnosine, L-Carnitine, and SCMC-Lys (S-carboxymethyl-L-cysteine Lysine salt H₂O).

5 Amino- and Hydroxyl-containing (including some investigational drugs): BN-82451, and Zeatin.

BENZODIAZEPINE TRANQUILIZERS AND HYPNOTICS:

Diazepam, Triazolam, Alprazolam, and the like.

ANTIULCER AGENTS:

10 Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Aldioxa, Benexate HCl, Cimetidine, Ebrotidine, Ecabapide, Esaprazole, Esomeprazole, Famotidine, Irsogladine, Lafutidine, Lansoprazole, Omeprazole, Pantoprazole, Pirenzepine, Polaprezinc, Rabeprazole, Ranitidine, Roxatidine, and Troxipide.

15 Hydroxyl (and Keto and Keto and/or Carboxyl) -containing: Enprostil, Misoprostol, Ornoprostil, Plaunotol, Rioprostil, Trimoprostil, and Oryzanol A.

Carboxyl-containing: Acetoxolone, Carbenoxolone, Rebamipide, and Sofalcone.

Amino (or Hydroxyl) - and Carboxyl-containing: Cetraxate, Ecabet, S-Methylmethionine, Rosaprostol, and Rotraxate.

Carbonyl-containing: Spizofurone, and Teprenone.

20 ANTICONVULSANTS:

Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Acetylpheneturide, Albutoin, *N*-benzyl-3-chloropropionamide, Carbamazepine, Cinromide, Clonazepam, Decimemide, Dimethadione, Doxenitoin, Ethosuximide, Ethotoin, Felbamate, Fosphenytoin, Lamotrigine, Levetiracetam, 25 Mephenytoin, Mephobarbital, Metharbital, Methetoin, Nitrazepam, Oxcarbazepine, Oxicarbamazepine, Phenacemide, Phenetharbital, Pheneturide, Phenobarbital, Phenylmethylbarbituric Acid, Phenytoin, Phethenylate Sodium, Primidone, Progabide, Remacemide, Rufmamide, Suclofenide, Sulthiame, Talampanel, Tetrantoin, Topiramate, Valpromide, Zonisamide, 5-Methyl-5-(3-phenanthryl)hydantoin, and 3-Methyl-5- 30 phenylhydantoin.

Hydroxyl-containing: Ganaxolone.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH): 4-Amino-3-hydroxybutyric Acid, Atrolactamide, and Buramate.

Carboxyl- and Amino-Containing (including Amide NH and Sulphonamide NH and Phosphomide NH): Gabapentin, Pregabalin, and Vigabatrin.

5 Carboxyl-containing: Tiagabine, and Valproic Acid.

ANTIPARKINSON'S: Levodopa & Carbidopa.

ANTIDEPRESSANT:

Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Amoxapine, Caroxazone, Demexiptiline, Desipramine,
10 Duloxetine, Fluoxetine, Fluvoxamine, Indalpine, Indeloxazine Hydrochloride, Iproclozide, Iproniazid, Isocarboxazid, Levophacetoperane, Maprotiline, Metapramine, Milnacipran, Minaprine, Moclobemide, Nialamide, Nomifensine, Nortriptyline, Octamoxin, Oxypertine, Paroxetine, Protriptyline, Reboxetine, Rolipram, Sertraline, Tofenacin, Tranylcypromine, Viloxazine, Benmoxine, and Rolicyprine.

15 Hydroxyl-containing: Befloxatone, Bupropion, Fenpentadiol, Hypericin, Opipramol, Pyrisuccideanol, Toloxatone, and Venlafaxine.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH): *S*-Adenosylmethionine, 5-Hydroxytryptophan, and Roxindole.

Carboxyl- and Amino-Containing (including Amide NH and Sulphonamide NH
20 and Phosphomide NH): Amineptine, and Tianeptine.

ANTI-HISTAMINIC

Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Antazoline, Astemizole, Clobenzepam, Desloratadine, Epinastine, Metron S, Mizolastine, and Tritoqualine.

25 Hydroxyl-containing: Terfenadine, and *N*-Hydroxyethylpromethazine Chloride.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphomide NH, etc.): Cetoxime.

Carboxyl-containing: Acrivastine, Bepotastine, Cetirizine, and Levocabastine,

Carboxyl- and Hydroxyl-containing: Fexofenadine.

30

ANTICANCER, ANTIOXIDATIVE, ANTIINFLAMMATORY, AND
CARDIOPROTECTIVE AGENT: Trans-Resveratrol [(E)-3,4',5-trihydroxystilbene).

ANTIDIABETIC: Metformin, andNateglinide/Glipizide/Glibenclamide (Glyburide).

It should be understood that while the lists of names of various categories of drugs
5 have been included above, such lists are presented in a way of illustration of the structural
features of the qualifying drugs in this invention and therefore, the number and types of
listed drugs are not necessarily limited thereto. In principal, any amino-, and /or carboxyl,
and/or carbonyl-, and/or hydroxyl-containing drug (from both known and investigational
drugs), irrespective of its therapeutic category and their mechanism of action, as listed in
10 drug databases such as Merck Index, prous science's ensemble, integrity, iddb, and the
like, are generally covered within the true spirit and scope of the present invention. For
clarity, in addition to the above lists of drugs, any amino-, and/or carboxyl-, and/or
carbonyl-, and/or hydroxyl-containing drug(s) (both known and investigational drugs)
from the following therapeutic areas are covered without any limitation:

15 CENTRAL NERVOUS SYSTEM: Sedatives, Hypnotics, Antidepressants,
Antipsychotics and Antimanics, Analgesics & Antipyretics, Antimigraine agents,
Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for
dementia, Antiemetics, drugs for Vertigo, CNS Stimulants & activators.

EYE: Antiinfective eye preparations, Antiinflammatory and antiallergic
20 preparations, antiglucoma drugs and other preparations to cure eye diseases.

EAR, NOSE and OROPHARYNX: Drugs used aural, nasal and oropharyngeal
preparation.

CARDIOVASCULAR SYSTEM: Antiarrhythmic drugs, Antihypertensives
(including alfa/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor
25 antagonists, diuretics, etc.), Antianginals (including nitrates, calcium channel blockers,
etc.), Drugs for cardiac failure and shock, Vasodilators, Coagulants, Anticoagulants,
Thrombolytics and antiplatelet drugs.

RESPIRATORY SYSTEM: Respiratory stimulants, Antitussives, Expectorants,
Mucolytics and Decongestants, Antihistamine agents, and antiasthmatics.

30 GASTRO INTESTINAL TRACT: Antiulcer and Antisecretory drags (including
H₂ receptor antagonists, Proton Pump Iinhibitors, Prostaglandin analogues, etc.),

Antacids, Antispasmodics and drugs modifying intestinal motility, Antidiarrhoeals (including antimotility and antimicrobial drugs) and drugs acting on gall bladder.

GENITO URINARY SYSTEM: Urinary antiinfectives, Diuretics, Urinary analgesics & antispasmodics, Antiinfective drugs acting on urethra and vagina, drugs acting on uterus, Drugs for prostatic hypertrophy (including alfa blockers and antiandrogens), Drugs for erectile dysfunction, and Spermicidal & nonhormonal contraceptives.

SKIN: Emollients and keratolytics, topical antiinfectives, topical antifungals, topical parasiticidals, topical steroids, topical drugs for acne vulgaris, drugs for psoriasis, pigmentation disorders, and Antiseborrhoeics.

MUSCULO-SKELETAL DISORDERS: Non Steroidal Anti Inflammatory Drugs (NSAIDs) including COX-2 inhibitors, Antiarthritic agents, Immunosuppressants, Topical analgesics, Muscle relaxants and Neuromuscular Drugs.

INFECTIONS AND INFESTATIONS: Penicillin antibiotics, Cephalosporin antibiotics, Quinolone & Fluoroquinolone antibiotics, Macrolide antibiotics, Chloramphenicol, Tetracycline antibiotics, Sulfonamides, Antianaerobics such as Metronidazole, Antitubercular drugs, Antileprosy drugs, Antifungals, Antiprotozoals, Anthelmintics & Antiinfestive Drugs, Antimalarials and Antivirals.

ENDOCRINE SYSTEM: Anabolic and androgenic steroids, Corticosteroids, Oestrogens, Progestogens and Hormonal contraceptives, Fertility Agents, Trophic hormones and related drugs, Thyroid and antithyroid drugs, Antidiabetics and hyperglycaemics.

NUTRITION: Vitamins, Amino acids, Anti-obesity drugs

METABOLISM: Hypolipidaemic drugs (including fibric acid derivatives, statins [(i.e., HMG CoA reductase inhibitors), nicotinic acid group, etc.], Drugs used for Gout and Drugs affecting bone metabolism (including bisphosphonates).

NEOPLASTIC DISORDERS: Anticancer drugs such as alkylating agents, cytotoxic antibiotics, antimetabolites such as cytarbine, Fludarbine, 5-Fluorouracil, Mercaptopurine, Thioguanine, etc., Vinca alkaloids and Etoposide, Taxanes, Topoisomerase 1 inhibitors, Cytotoxic immunosuppressants, Immunostmulants,

Cytoprotectives such as Amifostine, Oestrogens, Progestogens, hormon antagonists and other antineoplastic drugs.

ALLERGY AND IMMUNOLOGY: Antiallergics such as non-sedative antihistamines (e.g., Cetirizine, Desloratadine, Terfenadine, Fexofenadine, etc.), sedative
5 histamines and histamine receptor blockers.

ANAESTHETICS & SURGICALS: Local anaesthetics, intravenous anaesthetics, inhalation anaesthetics and muscle relaxants.

DRUG COMBINATIONS:

It is appreciated that NO-releasing prodrugs of any two or more drugs from the
10 above lists of potential drugs can be used in combination depending on the medical application/need. While a combination formulation may occasionally consist of more than two drugs (depending on the medical need), the following pairs of drugs are covered in this invention as illustrative pairs of candidate drugs for combination therapy.

ANTICANCER: Paclitaxel and Doxorubicin, Paclitaxel and Mitomycin C;
15 Paclitaxel and 9-aminocamptothecin, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP)/ 3-Aminopyridine-4-methyl-2-carboxaldehyde thiosemicarbazone (3-AMP) and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; CC-1065 and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; Trans-Resveratrol [(E)-
20 3,4',5-trihydroxystilbene) and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; Retinoic acid (including all trans-retinoic acid) and Butyric acid. Paclitaxel and Captopril, Doxorubicin and Biotin. 5-Fluorouracil and Cytarabine. Edatrexate and Paclitaxel; Cephalosporanic acid and Paclitaxel; Cephalosporin and Paclitaxel; and Paclitaxel and Gemcitabine,

25 ANTIPERKINSON'S: Levodopa and Carbidopa.

ANTIBIOTICS: Amoxicillin and Clavulanic acid; Ampicillin and Clavulanic acid, Amoxicillin and Pencillinic acid sulfone; Ampicillin and Pencillinic acid sulfone; Olivanic acid (or any carbapenem antibiotic) and a renal dipeptidase (dehydropeptidase I) inhibitor such as 3-substituted Z-2-acylamino propionic acid and the like.

ANTILIPIDEMIC AND HYPERTENSION: Lofibrol and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Ezetimibe and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin;

Amlodipine and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin.

5 ANTIDIABETIC: Metformin and Nateglinide/Glipizide/Glibenclamide (Glyburide)

ANTIDIABETIC AND HYPERTENSION: Metformin and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin.

10 ANTI-ASTHMATIC, ALLERGIC RHINITIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): Pseudoephedrine and Fexofenadine/Cetirizine/Desloratadine/Epinastine; Salbutamol and Ipratropium bromide; Mometasone and Formoterol/Salmeterol; Fluticasone and Formoterol/Salmeterol; Budesonide and Formoterol/Salmeterol.

15 ANTI-ARTHRITIS, INFLAMMATION AND ULCERS: Diclofenac (any known NSAID) and Misoprostol; Diclofenac (any known NSAID) and a proton pump inhibitor such as Omeprazole, Lansoprazole, Rabeprazole, Laminoprazole, Pantoprazole, and the like; A known antibacterial agent and a proton pump inhibitor such as Omeprazole, Lansoprazole, Rabeprazole, Laminoprazole, Pantoprazole, and the like; Naproxen (or any known NSAID) and Propfenazone; Acetaminophen and
20 chlorzoxazone/metaxalone/mephenoxalone.

ANTIVIRAL (HIV/AIDS, PEPATITIS B AND OTHER VIRAL INFECTIONS): Zidovudine and Lamivudine; Triple prodrug of Zidovudine; Lamivudine and Abacavir (Ziagen); Lopinavir and Ritonavir; Lamivudine and Adefovir or its prodrug adefovir dipivoxil; Amprenavir and Zidovudine; Nelfinavir and a nucleoside reverse transcriptase
25 inhibitor such as Zidovudine, Lamivudine, and the like; Stavudine and an antiretroviral agent such as Zidovudine, Lamivudine, and the like; Dideoxyinosine and an antiretroviral agent such as Zidovudine, Lamivudine, and the like; Emtricitabine and Penciclovir/Famciclovir; Acyclovir (or any other known antiviral compound) and a bile acid such as cholate, deoxycholate, chenodeoxycholate, and ursodeoxycholate (for
30 targeting bile acid transporters for enhanced oral bioavailability of the drug; Triple and prodrug of Zidovudine, Lamivudine and Efavirenz.

In addition to the above list of drugs, the the present invention also covers newer drugs with the above mentioned active functional groups as listed in the Merck index (13th edition) and other drug databases such as Prous Science's ensemble, integrity and the investigational drugs as listed in databases such as iddb, ensemble, integrity, and the like without any limitation.

It should be understood that either or both of any selected pair of drugs (in any proportion) can be in the form of nitrate ester (NO-releasing) prodrug(s) of formula (I) or pharmaceutically acceptable salts thereof and the other drug can be in its native form. For clarity, let us assume that Ibuprofen and Paracetamol are present as active principles in a pharmaceutical composition. Then, either or both of these drugs can be in their NO-releasing prodrug form (i.e., NO-Paracetamol and Ibuprofen/ Paracetamol and NO-Ibuprofen/ NO-Paracetamol and NO-Ibuprofen, etc.) and they can be present in any proportion.

It should also be understood that a pharmaceutical composition consisting of two or more of the above listed/qualified drugs, one of the drugs can be in the form of NO-releasing (nitrooxy derivative) prodrug and the other drug(s) in the combination can be in the form another type of prodrug(s).

It should also be understood that a pharmaceutical composition containing a combination of one of the above listed/qualified drug(s) and its own prodrug is also covered (i.e., a pharmaceutical composition consisting of NO-Paracetamol and Paracetamol in any proportion). In such pharmaceutical combinations, the free drug will be useful for faster onset of action and the prodrug will be useful for extension of the duration of action as it releases the drug in a controlled fashion over a longer period of time. Such combination drug therapy may also minimize the toxicity and other side effects due to excessive plasma concentration of free drug. It should also be understood that a pharmaceutical combination may contain a prodrug of one of the above listed/qualified drugs and an another type of prodrug of the same drug (i.e., NO prodrug of paracetamol and mutual prodrug of paracetamol with another drug) and these can be present in any therapeutic proportion depending on the medical need.

EXPERIMENTAL

ABBREVIATIONS USED:

BOP : Benzotriazol-1-yl-oxy- γ -(dimethylamino)phosphonium hexafluorophosphate

DMF: N,N-Dimethylformamide

5 DSC: N,N'-Disuccinimidyl carbonate

CDI: N,N'-Carbonyldiimidazole

DTE: Dithioerythritol

DTT: Dithiothreitol

DCC: N,N'-Dicyclohexylcarbodiimide

10 EDAC. HCl: 1-Ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride

HBTU: O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

TBTU: O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

EtOH: Ethanol

Et₂O: Diethyl ether

15 THF: Tetrahydrofuran

DMSO: Dimethyl sulfoxide

TEA: Triethylamine

DIPEA: N,N-Diisopropylethylamine

DCM: Dichloromethane

20 EtOAc: Ethyl acetate

DME: Dimethoxyethane

MeOH: Methanol

PE: Petroleum ether

RT: Room temperature

25 TFA: Trifluoroacetic acid

HOBT: N-Hydroxybenzotriazole

SYNTHETIC METHODS:

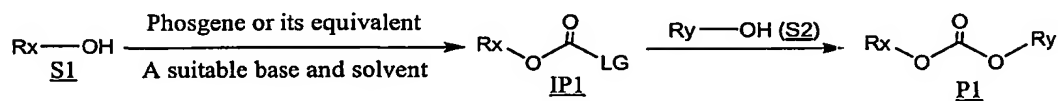
The prodrugs described herein can be prepared by any number of methods known/obvious to those skilled in the art. The synthetic approaches and the linkages are

30 chosen depending upon the functional groups such as carboxyl, hydroxyl, amino or carbonyl groups present in the drug molecules to be used. The following illustrative

methods, as shown in Schemes 1 through 9, can be utilized to make carbonate, urethane, amide, ester, N-acyl carbamate, N-acyl amide, N-acyl sulfamate, and N-acyl sulfonamide, N-acyl phosphoramidate, N-oxycarbonylsulfonamide, N-oxycarbonylcarbamate linkages, etc., between drug(s) and linker(s).

5 Methods of making carbonate linkage(s):

As depicted in the scheme 1, the carbonate linkage between the drug and the linker can be made by reacting the hydroxyl-containing drug (alternatively, hydroxyl group of the linker) with phosgene or its equivalents such as diphosgene, triphosgene, N,N'-carbonyldiimidazole (CDI), N,N'-disuccinimidyl carbonate (DSC), 4-nitrophenyl chloroformate and the like, to give a reactive alkoxycarbonyl derivative, where LG is suitable leaving group such as a halide, imidazole, O-succinimide, 4-nitrophenoxide and the like, which can be reacted with hydroxyl group of the linker (alternatively, hydroxyl group of drug if the linker is converted to active alkoxycarbonyl derivative) in the presence of a suitable base and solvent.



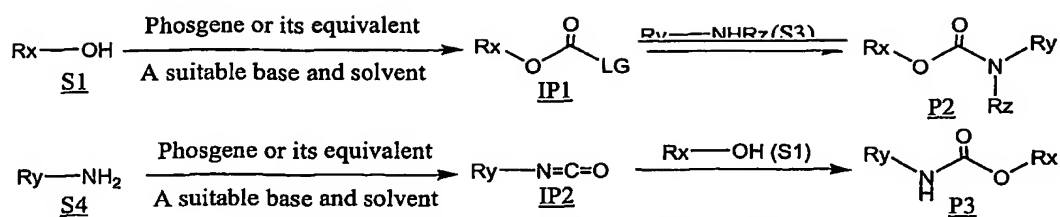
Rx and Ry are any monovalent organic radicals;

Scheme 1

Bases such as triethylamine, diisopropylethylamine, 4-(dimethylamino)pyridine (DMAP), and the like, can be used. Suitable solvents include CH_2Cl_2 , CHCl_3 , DMF, THF, ACN, ethyl acetate, ethyl ether and the like.

Method(s) of making urethane linkage(s):

As shown in scheme 2, the urethane linkage between the drug and the linker can be made by reacting the hydroxyl-containing linker with phosgene or its equivalents (defined above) to give a reactive alkoxycarbonyl derivative, which can be reacted with amino-containing drug in the presence of a suitable base and solvent. Alternatively, a urethane linkage can be made by adding an alcohol to an isocyanate.



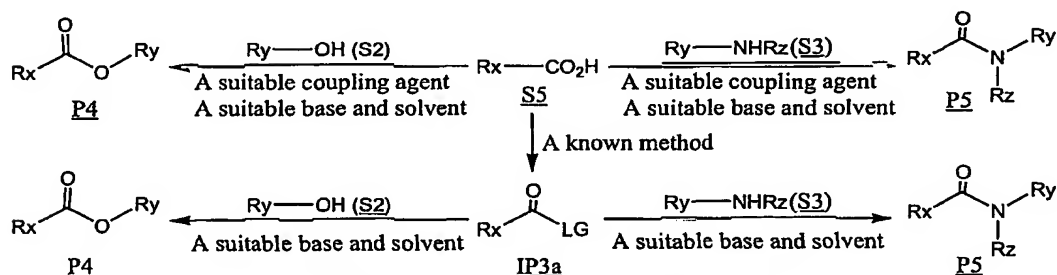
Rx, Ry, and Rz are any monovalent organic radicals;

Scheme 2

Suitable bases and solvents are same as defined above.

Method(s) of making amide or ester linkage(s):

As shown in the Scheme 3, an amide or ester linkage between the drug and the linker can be made by reacting a carboxyl-containing drug with an amino- or hydroxyl-containing linker in the presence of a suitable coupling agent, base and solvent. Alternatively, the carboxyl-containing compound can be first converted to reactive carbonyl derivative such as an acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolide and the like, which can be treated with amino-containing or hydroxyl-containing linker in the presence of a suitable base and solvent to afford the corresponding amide or ester linkage(s), respectively (see, Bodanszky, M. and Bodanszky, A., The Practice of Peptide Synthesis, Springer-Verlag, New York, 1984)



Rx, Ry, and Rz are any monovalent organic radicals;

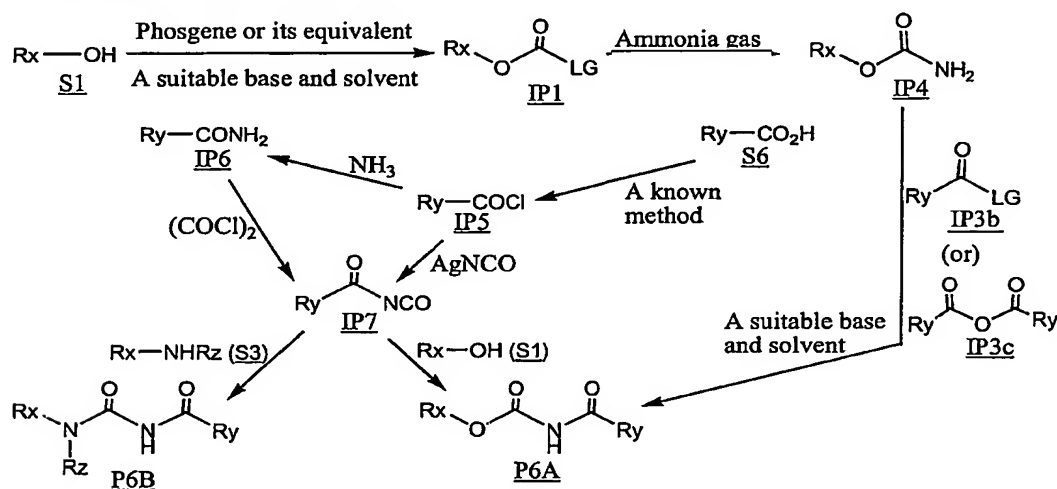
Scheme 3

Suitable coupling agents include DCC, EDCLHCl, BOP, HBTU, TBTU, DCC/HOBT, EDC/HOBT, and the like. Suitable bases and solvents are same as defined above.

Method(s) of making N-acyl carbamate and N-acyl urea linkage:

The linkage such as N-acyl carbamate linkage between the linker and drug can be made as shown in Scheme 4. Thus, treatment of an alcohol with phosgene or its

equivalent can yield the corresponding carbonochloridate, which upon treatment with ammonia gas can give the corresponding carbamate intermediate. The carbamate nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolidine, and the like, in the presence of a suitable base to yield the corresponding N-acyl carbamate. Alternatively, N-acyl carbamate can be made by the reaction of an alcohol with N-acyl isocyanate, which can be prepared either by the reaction of the corresponding amide with oxalyl chloride (See, Speziale, A. J. et al., J. Org. Chem. 1962, 27, 3142; Speziale, A. J. et al, J. Org. Chem. 1963, 28, 1805-1811) or by the reaction of the corresponding acid chloride with silver cyanate. (See, Hill, A.J. et al., J. Am. Chem. Soc, 1940, 62, 1595; Kim, D.K. J. Heterocyclic Chem. 1995, 32, 1625).

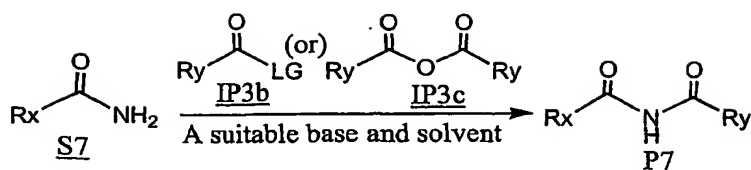


Scheme 4

Suitable bases and solvents are same as defined above.

Method(s) of making N-acyl amide linkage:

The N-acyl amide linkage between the linker and drug can be made as shown in Scheme 5. Thus, the amide nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolidine, and the like, in the presence of a suitable base to yield the corresponding N-acyl amide.



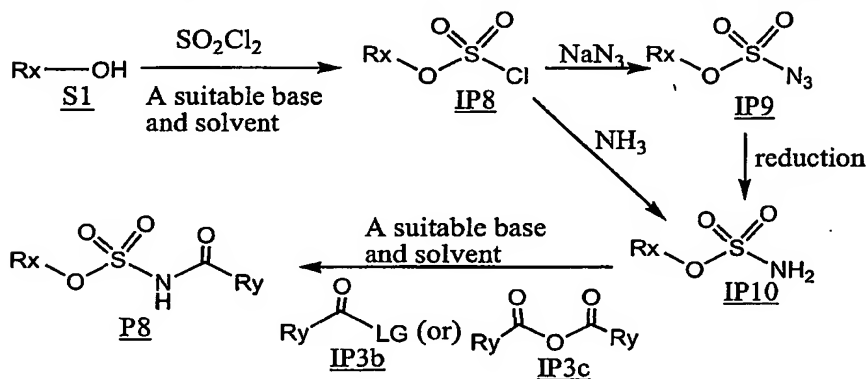
Rx and Ry are any monovalent organic radicals.

Scheme 5

Suitable bases and solvents are same as defined above.

Methods of making N-acyl sulfamate linkage:

The linkage such as N-acyl sulfamate between the linker and drug can be made as shown in Scheme 6. Thus, treatment of an alcohol with sulfuryl chloride in the presence of suitable base gives the intermediate sulfochloridate, which can be converted to the corresponding sulfamate. Acylation of sulfamate nitrogen with a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolidine, and the like, can yield the corresponding N-acyl sulfamate.



Rx and Ry are any monovalent organic radicals.

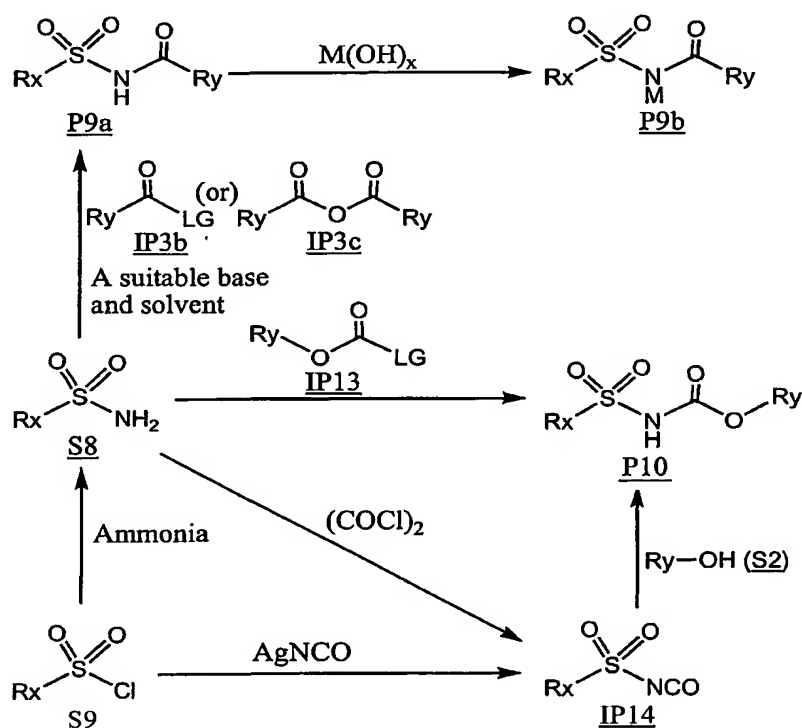
Scheme 6

Suitable bases and solvents are same as defined above.

Methods of making N-acyl/oxycarbonyl sulfonamide linkages:

The N-acyl/oxycarbonyl sulfonamide linkage between the linker and drug can be made as shown in Scheme 7. Thus, a sulfonamide nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazolidine, and the like, to yield the corresponding N-acylsulfonamide, which can be metallated using an inorganic base. Similarly, the

- 5 sulfonamide nitrogen can be acylated by a suitable formyl chloride derivative such as alkyloxycarbonyl chloride, imidazolidine and the like, to yield the corresponding N-alkyloxycarbonyl sulfonamide as shown in the scheme. Alternatively, the same linkage can be made by the reaction of an alcohol with sulfonyl isocyanate which can be prepared by known methods such as treatment of sulfonamide with oxalyl chloride (see, Hans Krzikalla et al., US2666787 or Smith, J. et al., J. Org. Chem. 1965, 30, 1260-1262) or by treatment of sulfonyl chloride with silver cyanate (See, Smith, J. et al., J. Org. Chem. 1965, 30, 1260-1262).



Rx, and Ry are any monovalent organic radicals; M is a metal ion; x is 1-4

Scheme 7

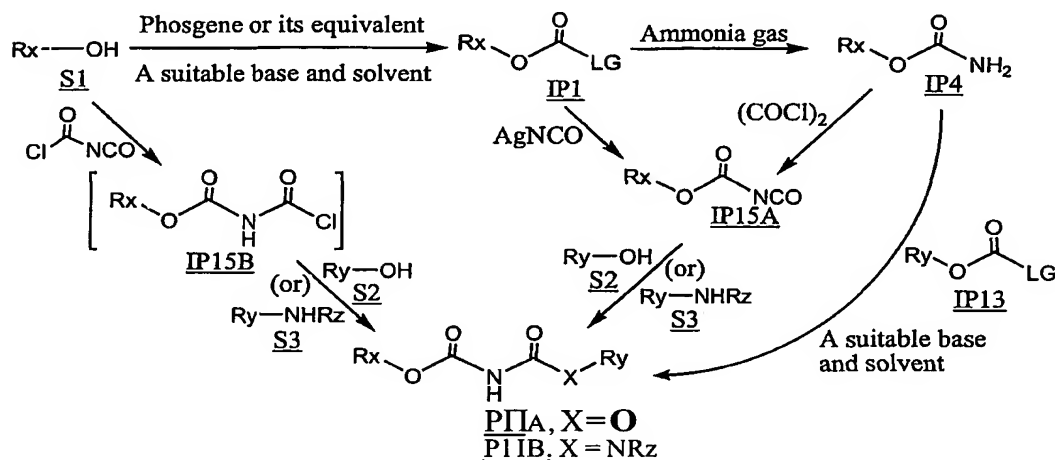
10

Suitable bases and solvents are same as defined above.

Method(s) of making N-oxycarbonylcarbamate and N-oxycarbonylurea linkages:

The N-oxycarbonylcarbamate (or N-oxycarbonylurea) linkage between the linker and drug can be made as shown in Scheme 8. Thus, carbamate nitrogen can be acylated by suitable formyl chloride derivatives such as alkyloxycarbonyl chloride,

imidazolidine and the like, to yield the corresponding N-alkyloxycarbonylcarbamate as shown in the scheme. Alternatively, the N-oxycarbonylcarbamate (or N-oxycarbonylurea) linkage between the linker and drug can be made by the reaction of an alcohol (or an amine) with carbamoyl isocyanate (IP15A), which can be prepared by known methods such as by treatment of carbamate with oxalyl chloride (See, Grehn L, et al, Synthesis, 1988, 922-994) or by treatment of a formyl chloride with silver cyanate (See, Kim, D.K. et al., J. Heterocyclic Chem. 1995, 32, 1625). Alternatively, N-oxycarbonylcarbamate (or N-oxycarbonylurea) can be prepared in two steps. Step 1: reaction of an alcohol or phenol with chlorocarbonyl isocyanate to give N-oxycarbonyl carbamoyl chloride intermediate (IP15B). Step 2: reaction of the intermediate IP15B with the same or another alcohol or phenol or an amine. (For a review on chemistry of chlorocarbonyl isocyanate, see, Gorbatenko, V.I. Tetrahedron, 1993, 49, 3227).



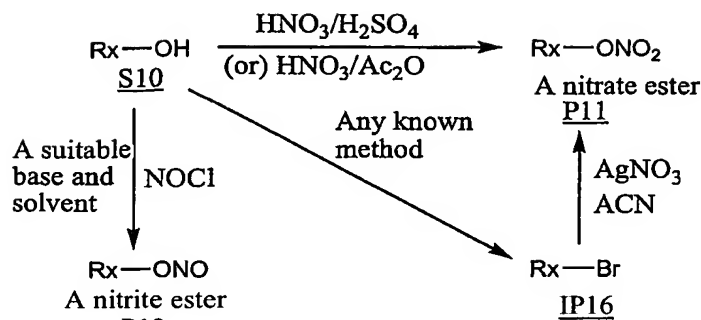
Rx, Ry and Rz are any monovalent organic radicals.

Scheme 8

Suitable bases and solvents are same as defined above.

15 Method(s) of making Nitrate CnitrooXyl or Nitrite (nitrosyloxy) esters:

The nitrate or nitrite esters can be made as shown in Scheme 9. Thus, a nitrate or nitrite ester can be made by treating an alcohol with $\text{HNO}_3/\text{H}_2\text{SO}_4$ (or $\text{HNO}_3/\text{Ac}_2\text{O}$) or nitrosyl chloride, respectively. Alternatively, a nitrate ester can be made by treating a halide (bromide or iodide is preferred) with silver nitrate in a polar aprotic solvent such as acetonitrile.



Rx is any monovalent organic radical.

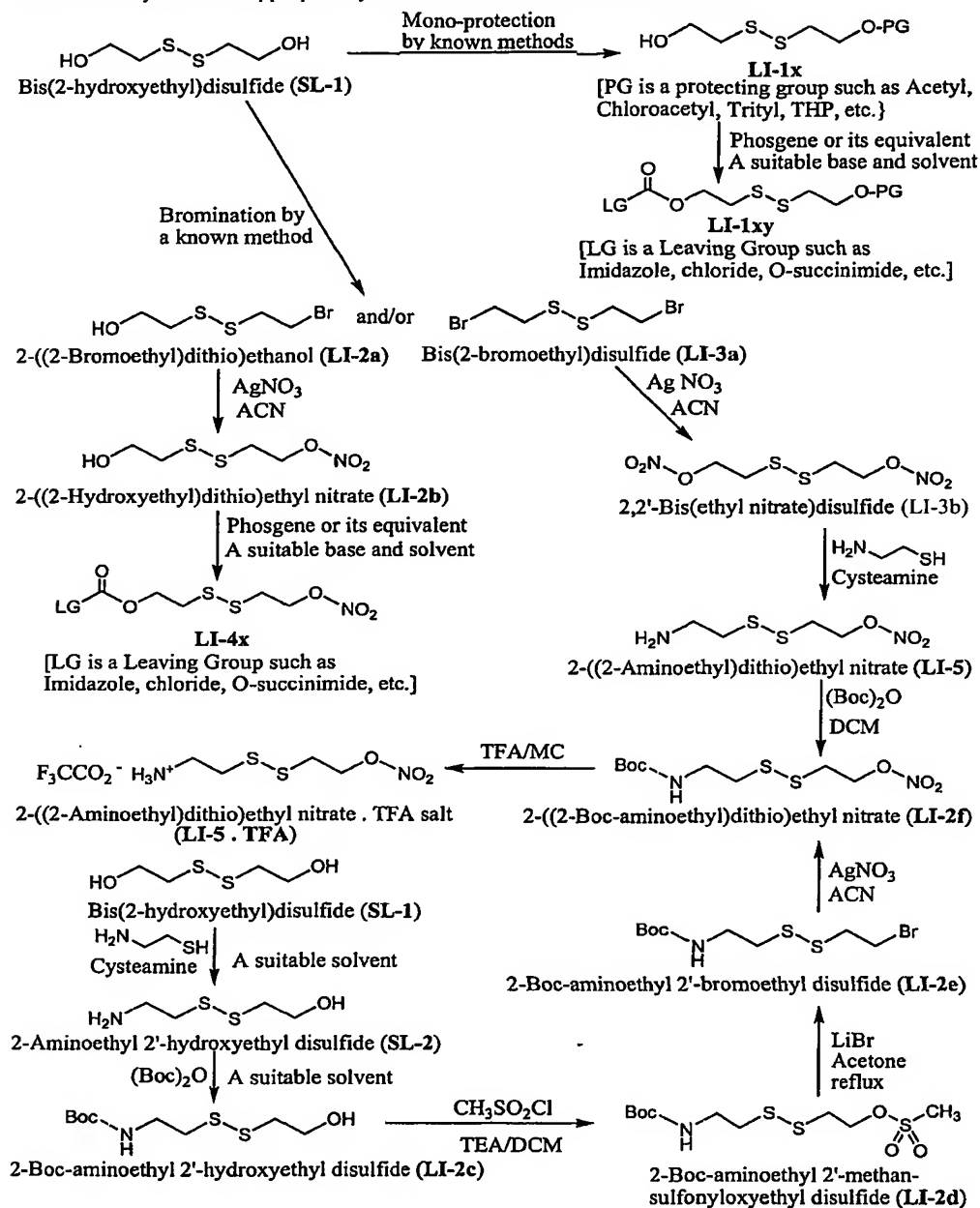
Scheme 9

Compounds (Prodrugs) of the formula (I) containing bio-cleavable linkers and linkages can be synthesized by various methods obvious to those skilled in the art. As a matter of illustration, any of the approaches shown in the following schemes can be used to make such prodrugs of the formula (I) described herein.

Monoprotection of diol or aminoalcohol or diamino compounds [i.e., linker(s)] with suitable protecting groups and their selective removal at appropriate stage of the synthesis are carried out as described in Theodora W. Greene and Peter G.M. Wuts, "Protective Groups in Organic Synthesis", 3rd edition, John Wiley and Sons, Inc. New York (1999), the disclosures of which are incorporated herein by reference. Suitable protecting groups (PGs) include, but not limited to, acetyl, Boc, Fmoc, benzoyl, pivaloyl, trityl, tetrahydropyranyl (THP), and silyl (TBDMS, TMS, etc.). Obviously, selection of a suitable protecting group is very crucial for the success of a chosen method for the synthesis of prodrugs described in this invention.

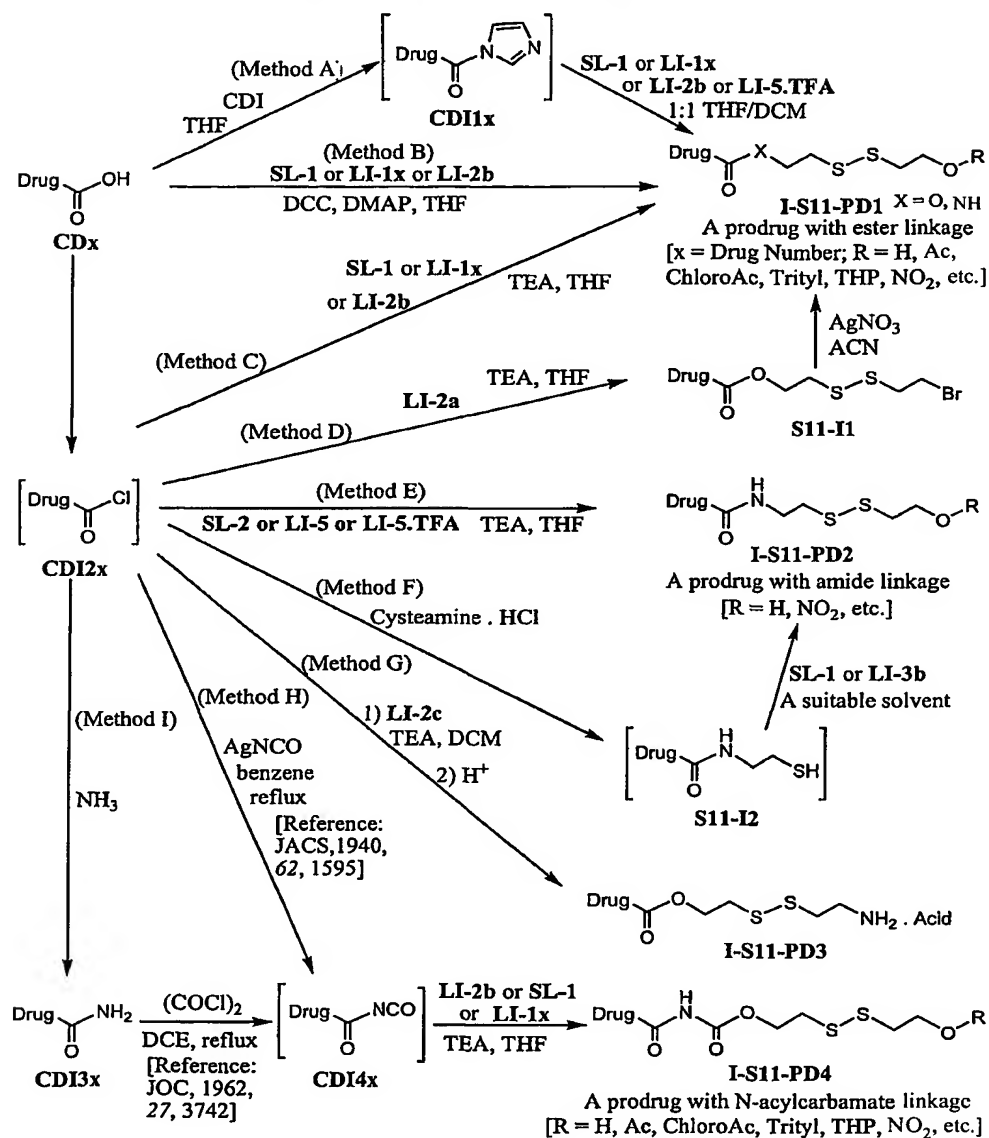
Synthesis of appropriately derivatized/modified bio-labile linker is shown in Scheme 10.

Scheme 10: Synthesis of appropriately derivatized/modified linker intermediates

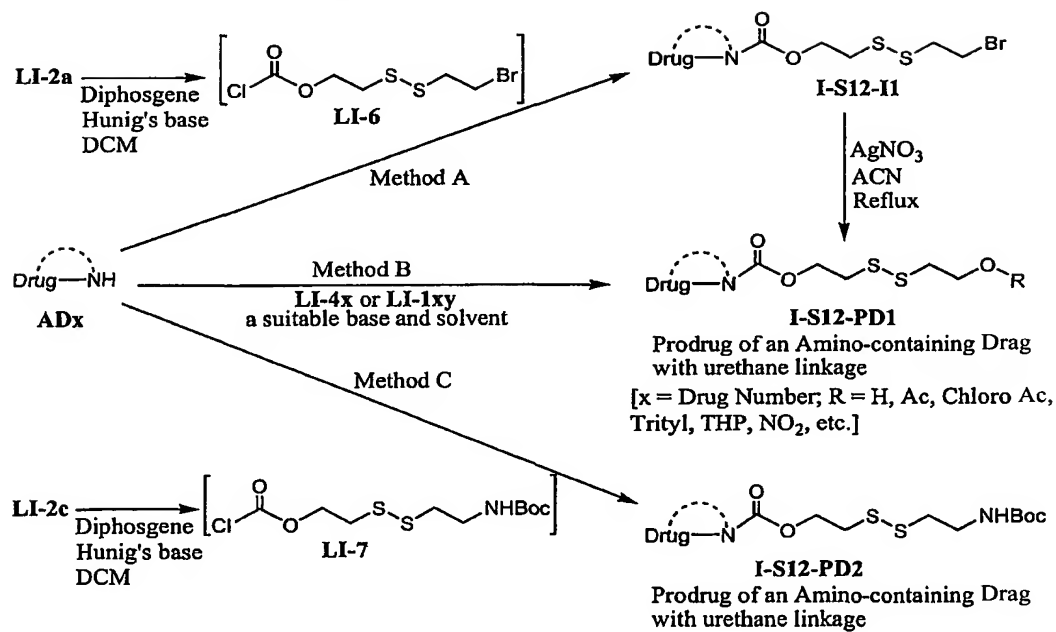


Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs) of carboxyl-, amino-, and hydroxyl-containing drugs are shown in Schemes 11 through 14.

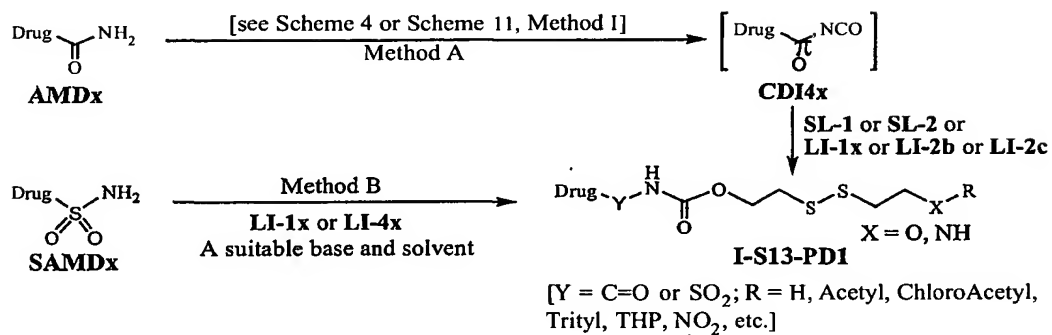
Scheme 11: Synthesis of Prodrugs of Carboxyl-containing Drugs



Scheme 12: Synthesis of Prodrugs of Amino-containing Drugs



Scheme 13: Synthesis of Prodrugs of Amide/Sulfonamide-containing Drugs:

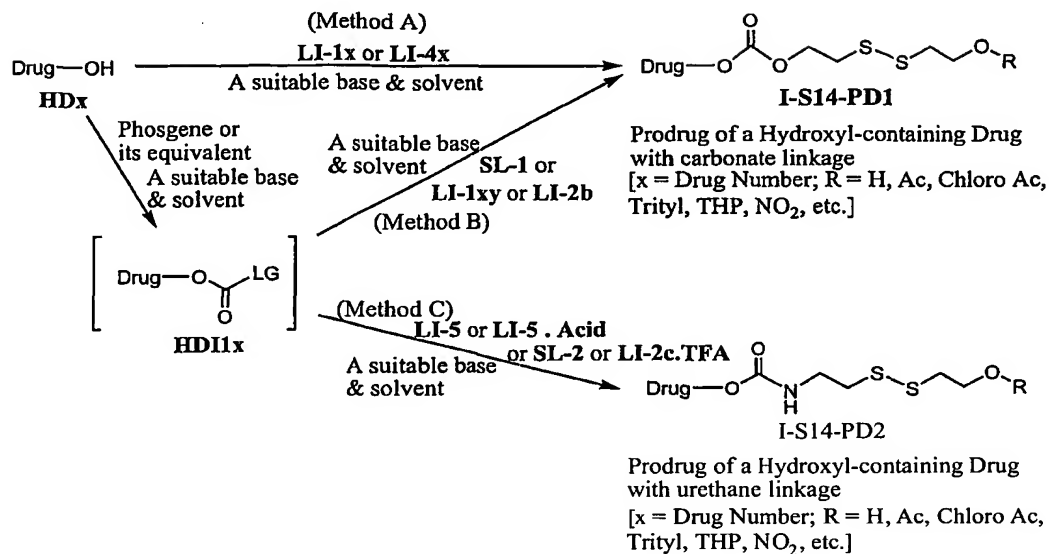


Prodrug of an Amide/Sulfonamide-containing Drug
with N-oxycarbonylamide/sulfonamide linkage

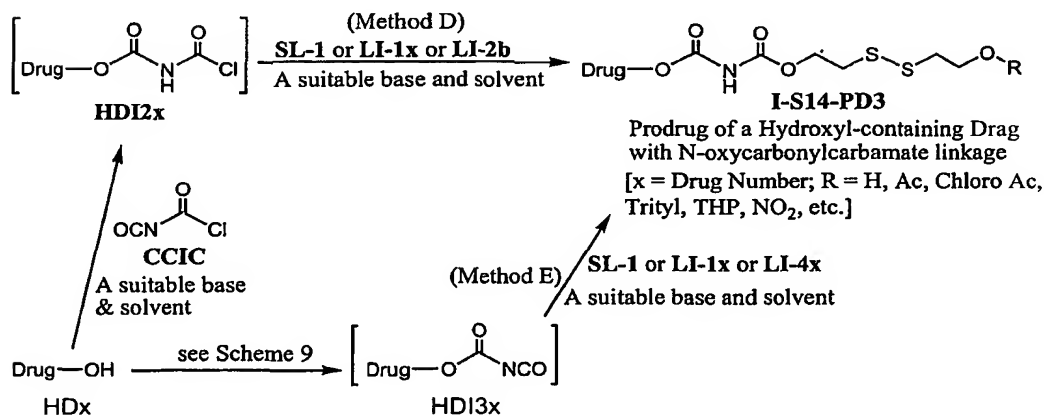
AMDx is a CONH₂-containing drugs such as vapromide, levotiracetam, carbamazepine, and the like.
SAMDx is a SO₂NH₂-containing drugs such as valdecoxib, celecoxib, and the like.

Scheme 14: Synthesis of Prodrugs of Hydroxyl-containing Drugs

A) Prodrugs with carbonate and carbamate linkages:

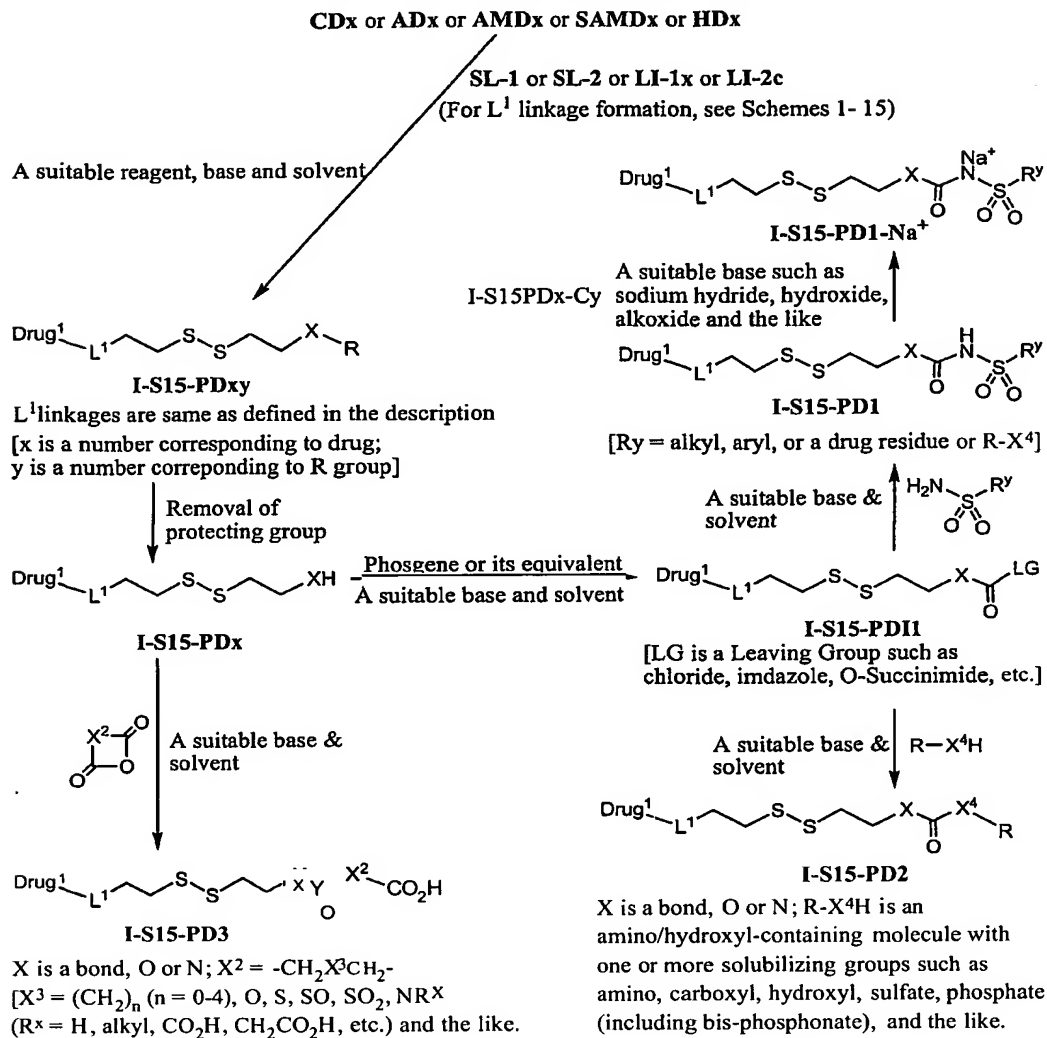


B) Prodrugs with N-oxycarbonylcarbamate linkage:

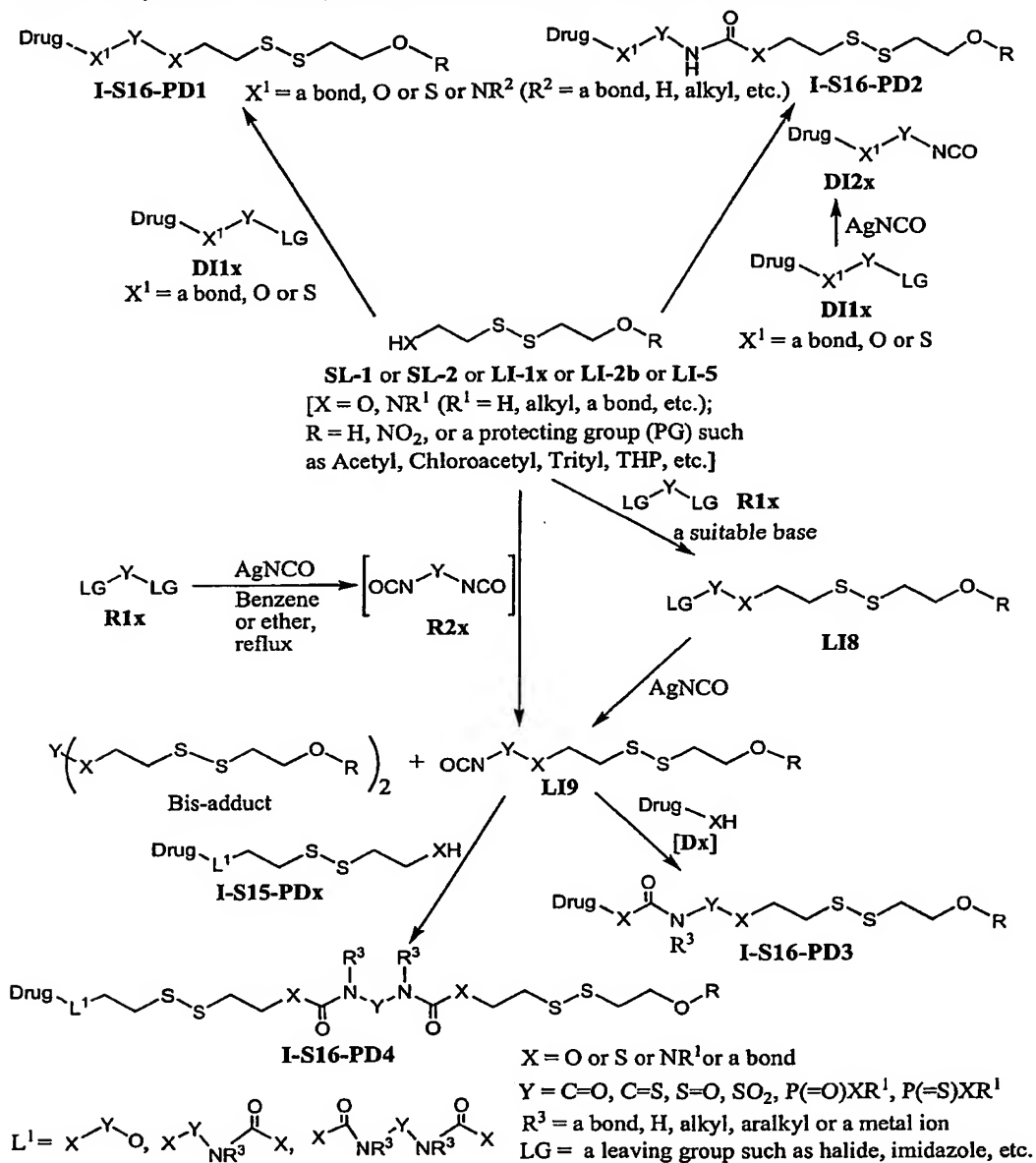


Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs and water-soluble prodrugs) are shown in Schemes 15 and 16.

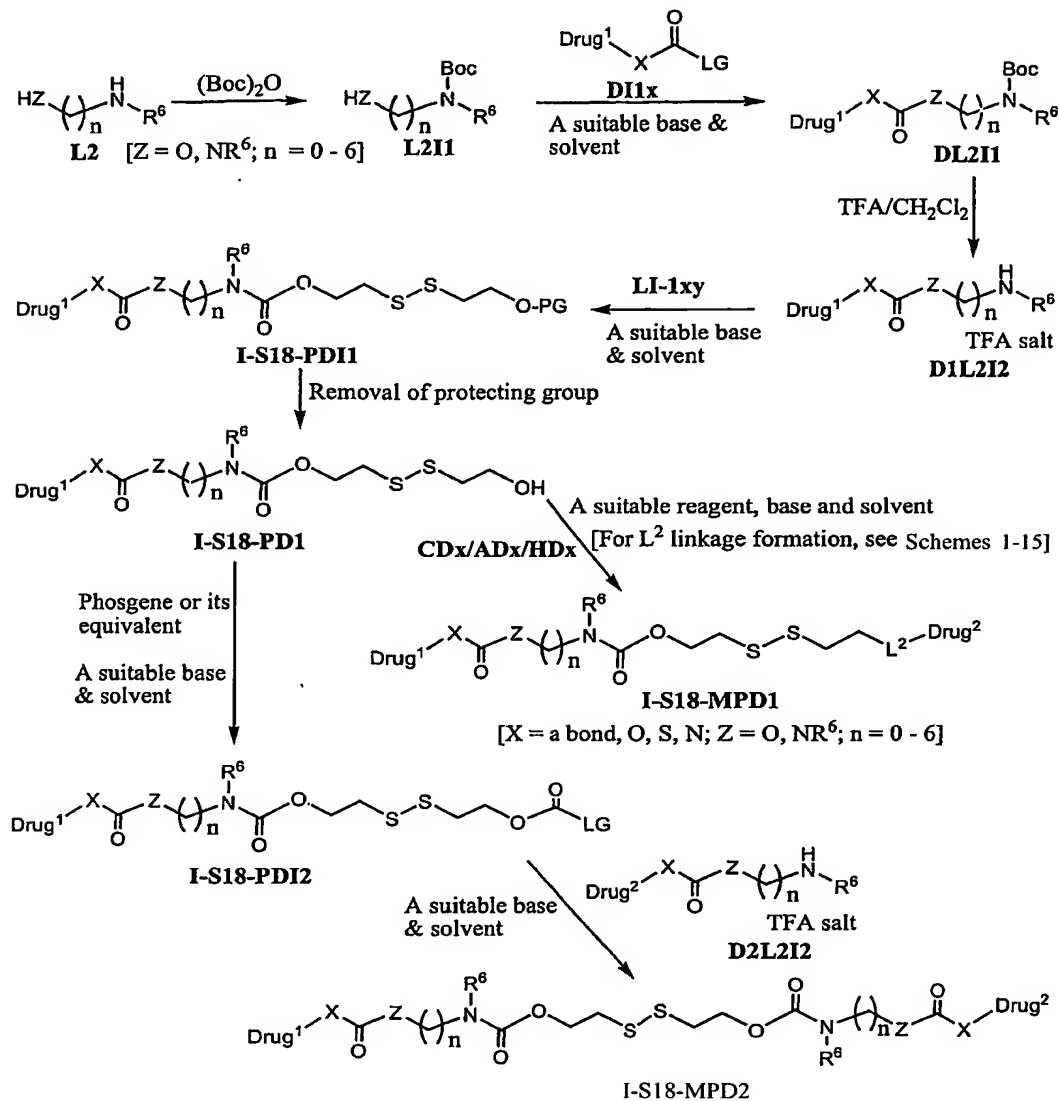
Scheme 15: Synthesis of Water-soluble Prodrug(s) using a bio-cleavable linker(s) and spacer linker (s)



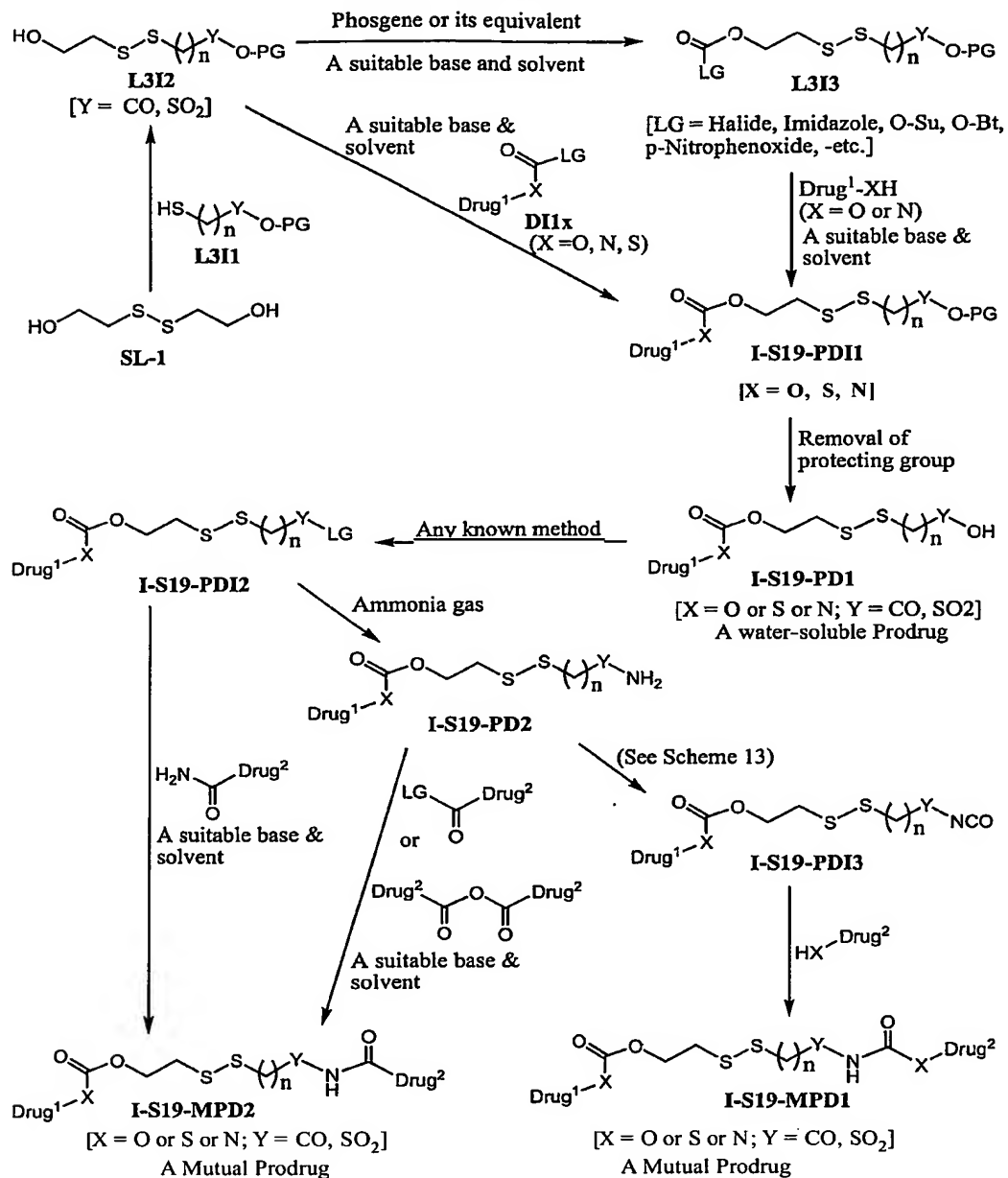
Scheme 16: Synthesis of Prodrugs containing a biocleavable linker and various types linkages



Scheme 18: Synthesis of Double/Mutual Prodrug(s) with additional linkers

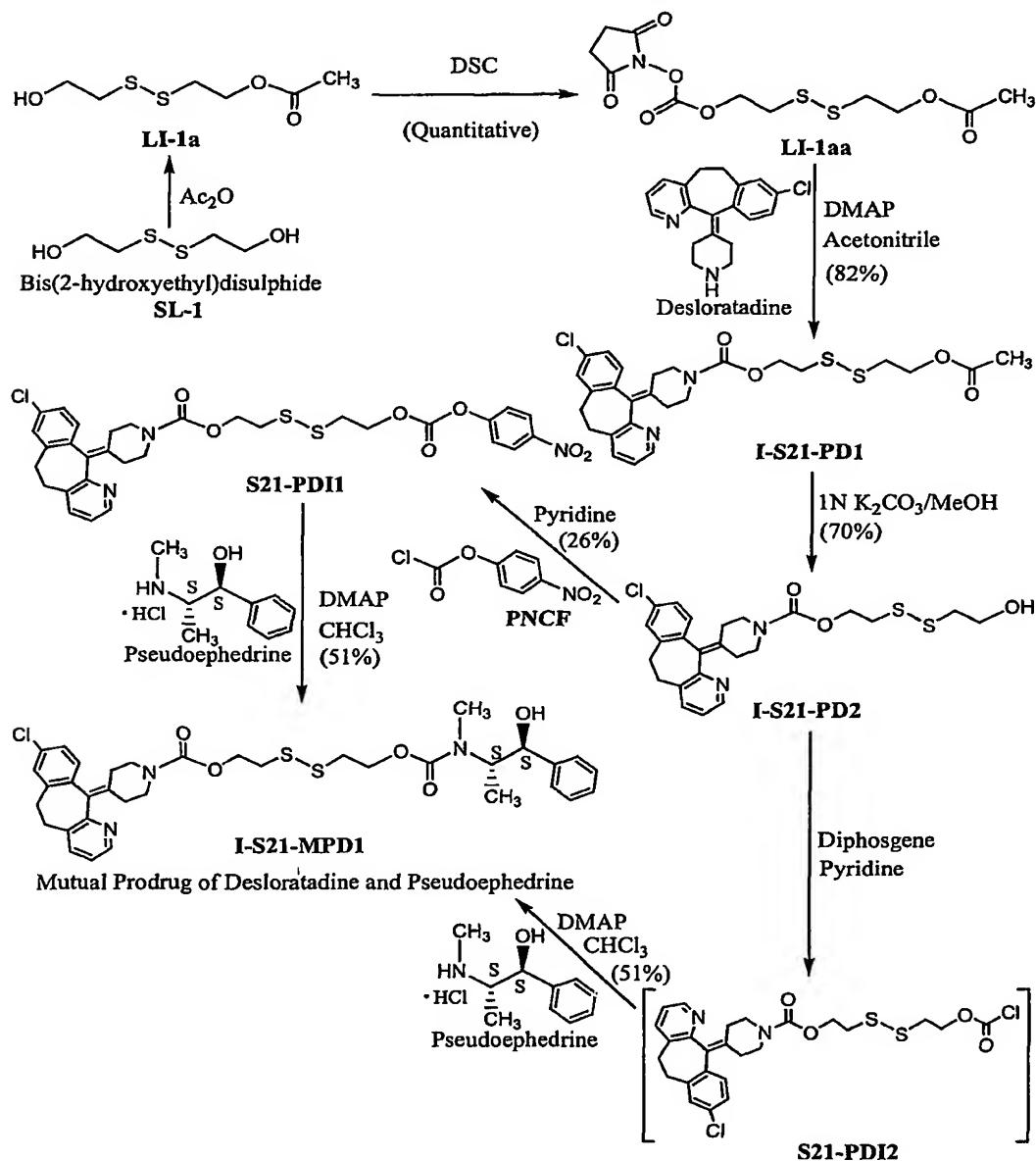


Scheme 19: Synthesis of Mutual Prodrug(s) using modified bio-cleavable linker(s)

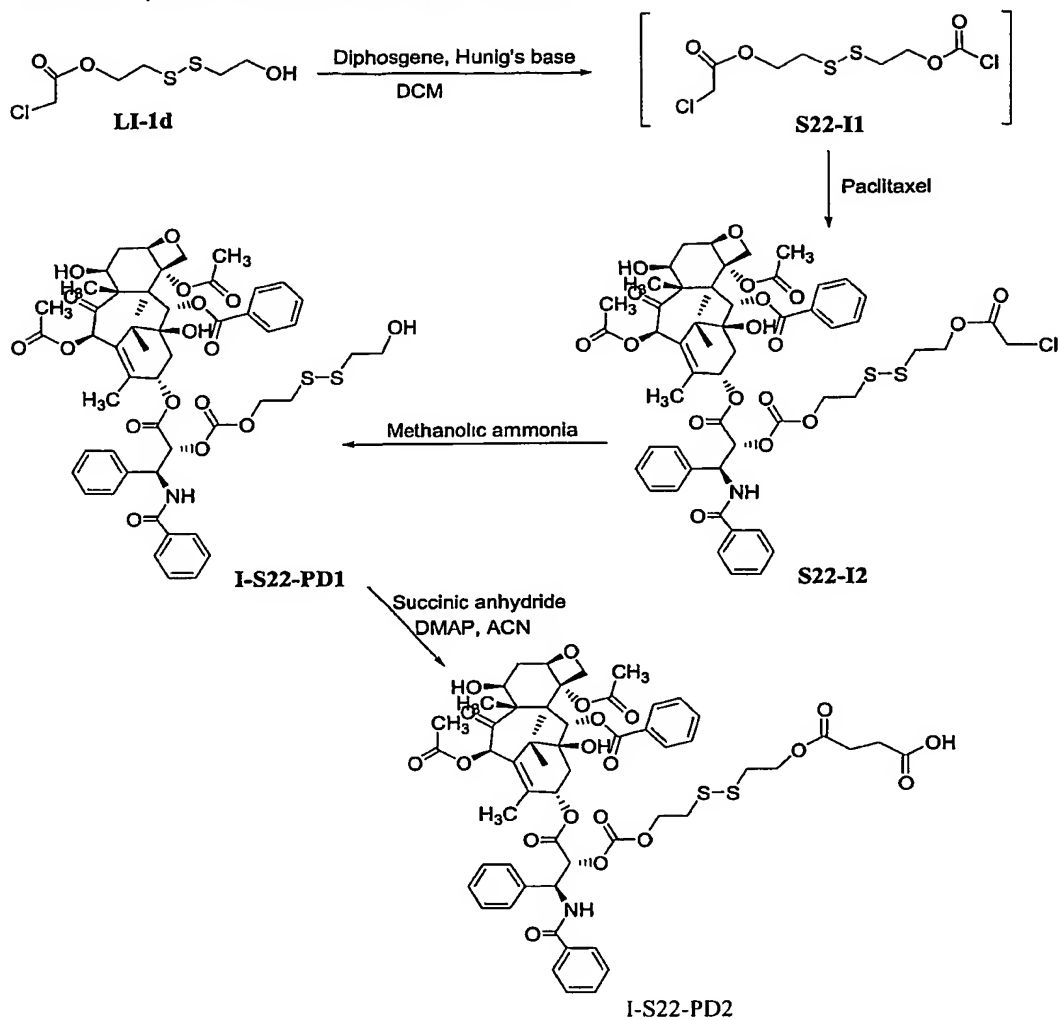


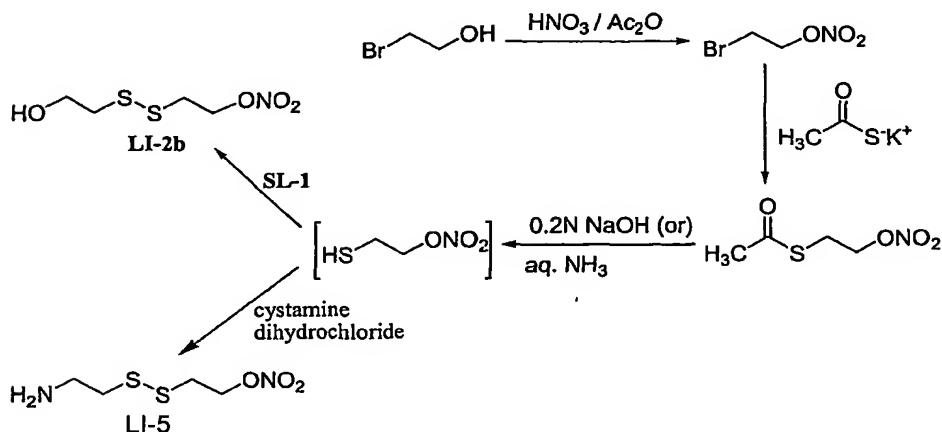
As a matter of illustration, mutual prodrug of desloratadine and pseudoephedrine was synthesized as depicted in Scheme 21.

Scheme 21: A Mutual Prodrug of Desloratadine and Pseudoephedrine



Scheme 22: Synthesis of a water-soluble prodrug of paclitaxel



Scheme 24: An alternative method for the synthesis of Linker Intermediates **LI-2b** and **LI-5****Example 1**

Synthesis of 2-[(2-hydroxyethyl)dithio]ethyl acetate (**LI-1a**):

Acetic anhydride (5.67 ml, 56.87 mmol) and pyridine (40.4 ml, 499 mmol) were added to a solution of 2-(hydroxyethyl)disulfide (**SL-I**, 15.39 g, 99.78 mmol) in DCM (350 mL) at RT and the mixture was stirred at RT for 16 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 8.16 g (42%) of **LI-1a** as a pale yellow oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.00 (bs, 1H), 2.08(s, 3H), 2.80-2.95 (m, 4H), 3.89 (t, 2H, $J = 6$ Hz), 4.35 (t, 2H, $J = 6$ Hz), MS: (m/z) 219 $[\text{M}]^+$.

Example 2

Synthesis of 2-[[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]dithio] ethanol (**LI-1b**):

This compound was synthesized by a method described by K. F. Bernady *et al.*, *J. Org. Chem.*, 1979, 44, 1438. Dihydropyran (8.41 g, 100 mmol) was added to a solution of **SL-1** (15.4 g, 100 mmol) in DCM (200 mL) at 0-5 $^\circ\text{C}$, followed by PTSA (-5%) and stirred at RT for 5 h. The mixture, after usual aqueous work-up and chromatographic purification, afforded 14.5 g (50%) of **LI-1b**. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.5-1.9 (m, 6H), 2.88 (t, 2H, $J = 6$ Hz), 2.94 (t, 2H, $J = 6$ Hz), 3.45-3.57 (m, 1H), 3.67-3.78 (m, 1H), 3.85-4.05 (m, 2H), 3.90 (t, 2H, $J = 6$ Hz), 4.65 (s, 1H).

Example 3

Synthesis of 2-[[2-(Trityloxy)ethyl]dithio] ethanol (**LI-1c**):

This compound was synthesized by a method described by O. Hernandez *et al*, *Tetrahedron Letters*, **1981**, 22, 1491-1494. Thus, 8.58 g (21.4 mmol) of 4-dimethylamino-N-triphenylmethylpyridinium chloride (A.V. Bhatia *et al*., *Organic Synthesis*, 1997, 75, 184-185) was added to a solution of **SL-I** (3.0 g, 19.45 mmol) in DCM (90 mL) and stirred at RT for 24 h. The mixture, after usual aqueous work-up and chromatographic purification, afforded 2.86 g (37%) of **LI-Ic**. ¹H-NMR (300 MHz, CDCl₃): δ 2.70 (t, 2H, J = 6.0 Hz), 2.88 (t, 2H, J = 6.0 Hz), 3.39 (t, 2H, J = 6.0 Hz), 3.80 (q, 2H, J = 6.0 Hz), 7.24-7.33 (m, 10H), 7.44-7.46 (m, 5H). MS (m/z): 396 [M]⁺.

Example 4

10 Synthesis of chloroacetic acid 2-(2-hydroxyethyl)disulfanyl)ethyl ester (**LI-Id**):

To a solution of **SL-I** (23 g, 150 mmol) in DCM (250 mL) at 0 °C were added TEA (10.12 g, 100 mmol) and chloroacetyl chloride (11.3 g, 100 mmol) and stirred overnight at RT. The reaction mixture was concentrated and purified by column chromatography to afford 8.3 g (37%) of **LI-Id**. ¹H-NMR (300 MHz, CDCl₃): δ 2.88 (t, 2H, J = 5.7 Hz),
15 2.95 (t, 2H, J = 6.6 Hz), 3.89 (t, 2H, J = 5.7 Hz), 4.09 (s, 2H), 4.47 (t, 2H, J = 6.6 Hz).

Example 5

Synthesis of 2-((2-hydroxyethyl)dithio)ethyl nitrate (**LI-2b**) and 2,2'-bis(ethyl nitrate)disulfide (**LI-3b**):

These intermediates were synthesized in two steps as shown in Scheme 10.

20 Step 1: Synthesis of 2-((2-bromoethyl)dithio)ethanol (**LI-2a**) and bis(2-bromoethyl)disulfide (**LI-3a**): These compounds can be synthesized *via* bromination of **SL-I** by a known bromination method. (For a suitable bromination method, see Fruniss, B.S. *et al*., Vogel's Text Book of Practical Organic Chemistry, 5th edition, Pearson Education, Singapore, 1989; pp 559-579). The following methods were explored:

25 Method 1: To a solution of **SL-I** (15g, 97.4 mmol) in DMF (50 mL) was added PPh₃ (25.5g, 97.4 mmol) and cooled to 0 °C. Bromine (3.33 mL, 64.9 mmol) was added drop-wise and stirred at RT for 18 h. TLC of the mixture showed the mono-bromo derivative **LI-2a** as the major product with only trace amounts of dibromide **LI-3a**. The mixture was diluted with water and extracted with EtOAc. After usual aqueous work-up and
30 chromatographic purification, 3.65 g (26%) of **LI-2a** were obtained. ¹H-NMR (300 MHz,

CDCl_3 : δ 1.82 (s, 1H), 2.88 (t, 2H, $J = 5.8$ Hz), 3.08 (t, 2H, $J = 7.90$ Hz), 3.63 (t, 2H, $J = 7.90$ Hz), 3.90 (t, 2H, $J = 5.8$ Hz).

Method 2: To a solution of **SL-I** (40 g, 0.26 mol) in DCM (400 mL) at 0 °C was added a solution of PBr_3 (24.62 mL, 0.26 mol) in DCM (50 mL) and the mixture was stirred at
5 RT for 15 h. TLC indicated formation of **LI-3a** as the major product with trace amounts of **LI-2a**. The reaction was quenched by the addition of water and extracted with DCM. After usual aqueous work-up and chromatographic purification, 33 g (45.3%) of **LI-3a** were obtained. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 3.1-3.15 (m, 4H), 3.60-3.66 (m, 4H). MS (Cl^+) m/z : 277.69 $[\text{M}+\text{H}]^+$, 279.66. An alternative synthesis of **LI-3a** has been reported.
10 (Sharma, M. *et al*, *Bioorg. Med. Chem. Lett.*, 2004, 14, 5347-5350).

Method 3: To a cold suspension of **SL-I** (20 g, 129 mmol) in DCM (400 mL) was added CBr_4 (42 g, 129 mmol) and stirred for 10 min. PPh_3 (34 g, 129 mmol) was then added and stirred at RT for 14 h. The reaction mixture was concentrated and the residue purified by column chromatography to give 13.5 g (52.3%) of **LI-2a** and 13.0 g (36%) of **LI-3a**.
15 These compounds were identical (by TLC, NMR and MS) to those obtained in Methods 1 and 2 described above.

Synthesis of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b): To a solution of **LI-2a** (2g, 9.21 mmol) in acetonitrile (15 mL) was added AgNO_3 (1.88g, 11.05 mmol) portion-wise and the mixture was stirred at RT in the dark for 45 min. The reaction mixture was
20 filtered through celite and the filtrate was concentrated. The residue, after usual aqueous work-up and chromatographic purification gave 1.46 g (74%) crude **LI-2b** which was used for the next reaction without further purification. An analytical sample was obtained by chromatographic purification. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.89 (t, 2H, $J = 6.0$ Hz), 2.98 (t, 2H, $J = 7.5$ Hz), 3.90 (t, 2H, $J = 6.0$ Hz), 4.74 (t, 2H, $J = 7.5$ Hz); MS (EI^+)
25 (m/z): 199 $[\text{M}]^+$.

Synthesis of 2,2'-bis(ethyl nitrate)disulfide (LI-3b): AgNO_3 (8.01 g, 47.12 mmol) was added portion-wise to a solution of **LI-3a** (6.0 g, 21.42 mmol) in acetonitrile (40 mL) at RT in the dark and stirred for 30 min. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* at 35 °C to afford 4.6 g (88%) of **LI-3b**, which was
30 used without further purification. An analytical sample was obtained by chromatographic

purification (3-15% EtOAc in petroleum ether). $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.10 (t, 4H, $J = 6.7$ Hz), 4.71 (t, 4H, $J = 6.7$ Hz). MS (EI) $^+$ m/z : 244 $[\text{M}]^+$.

Example 6

Synthesis of tert-butyl 2-[(2-hydroxyethyl)dithio]ethylcarbamate (**LI-2c**): To a solution of cysteamine hydrochloride (15 g, 132 mmol) in MeOH (130 mL) at 0-5 $^\circ\text{C}$ was added TEA (37 mL, 264 mmol), followed by a solution of **SL-I** (20.4 g, 132 mmol) in DCM (50 mL) and stirred at RT for 6 h. The mixture, which contained the intermediate **SL-2**, was cooled and $(\text{Boc})_2\text{O}$ (63.4 g, 290.4 mmol) was added and stirred overnight. MeOH was removed under vacuum. After usual aqueous work-up and chromatographic purification, **LI-2c** was obtained as a colorless oil (14.6 g, 44%).

The above linker intermediate can also be prepared by the following method:

Step 1: TEA (37 mL, 264 mmol) and a solution of $(\text{Boc})_2\text{O}$ (48 g, 220 mmol) in DCM (100 mL) were added to a suspension of cystamine dihydrochloride (20 g, 88.8 mmol) in DCM (300 mL) and stirred at RT for 15 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 30 g (96%) of tert-butyl 2-({2-[(tet-butoxycarbonyl)amino]ethyl}dithio)ethylcarbamate as a white solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.43 (s, 18H), 2.78 (t, 4H, $J = 6.3\text{Hz}$), 3.44 (q, 4H, $J = 6.0$ Hz), 5.00 (bs, 1H). MS (m/z): 353.18 $[\text{M}+\text{H}]^+$, 375.24 $[\text{M}+\text{Na}]^+$.

Step 2: A solution of 2-mercaptoethanol (1.44 g, 18.5 mmol) in DCM (10 mL) was added to a mixture of tert-butyl 2-({2-[(tert-butoxycarbonyl)amino]ethyl}dithio)ethyl carbamate (5.0 g, 14.2 mmol) and TEA (3.87 mL, 27.7 mmol) in DCM (30 mL) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 2.0 g (56%) of **LI-2c** was obtained. $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 1.43 (s, 9H), 2.79 (t, 2H, $J = 6.5\text{Hz}$), 2.87 (t, 2H, $J = 5.7\text{Hz}$), 3.48 (q, 2H, $J = 6\text{Hz}$), 3.88 (t, 2H, $J = 5.5$ Hz), 4.8 (bs, 1H). MS (m/z): 254 $[\text{M}+\text{H}]^+$, 276.13 $[\text{M}+\text{Na}]^+$.

Removal of the Boc group of **LI-2c** was accomplished as described in Example 10 to afford the TFA salt, **LI-2c.TFA**.

Obviously, the linker intermediates **LI-2b** and **LI-2c** can also be synthesized by following the method outlined in Scheme 24.

Example 7

Synthesis of 2-Boc-aminoethyl-2'-methanesulfonyloxyethyl disulfide (**LI-2d**): To an ice-cold solution of **LI-2c** (9 g, 35.52 mmol) in DCM (80 mL) and TEA (9.9 mL, 71.04 mmol) was added methanesulfonyl chloride (4.2 mL, 53.28 mmol). The reaction mixture was stirred at 0-5 °C for 45 min, then diluted with DCM. After usual aqueous work-up and chromatographic purification, 13.38 g of **LI-2d** were obtained, which was pure enough for further use. ¹H-NMR (300 MHz, CDCl₃): δ 1.43 (s, 9H), 2.80 (t, 2H, J = 6.4 Hz), 2.98 (t, 2H, 5.7 Hz), 3.05 (s, 3H), 3.35-3.45 (m, 2H), 4.45 (t, 2H, J = 6.7 Hz), 4.78 (br s, 1H).

Example 8

Synthesis of 2-Boc-aminoethyl-2'-bromoethyl disulfide (**LI-2e**): To a solution of **LI-2d** (13 g, 39.27 mmol) in acetone (100 mL) at RT was added LiBr (6.82 g, 78.54 mmol) and stirred under reflux for 1 h. The reaction mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 8.8 g (78%) of **LI-2e**. ¹H-NMR (300 MHz, CDCl₃): δ 1.44 (s, 9H), 2.80 (t, 2H, J = 6.32 Hz), 3.06 (t, 2H, J = 6.73 Hz), 3.44 (q, 2H), 3.61 (t, 2H, J = 7.62 Hz), 4.87 (br s, 1H). MS (EI)⁺ m/z: 317 [M+H]⁺.

Example 9

Synthesis of 2-((2-Boc-aminoethyl)dithio)ethyl nitrate (**LI-2f**): To a solution of **LI-2e** (8 g, 25.3 mmol) in acetonitrile (80 mL) was added AgNO₃ (5.16 g, 30.36 mmol) portion-wise and stirred at RT for 1 h in the dark. The mixture was filtered through celite and the filtrate was concentrated. The residue obtained was purified by column chromatography to afford 6.34 g (84%) of **LI-2f**. ¹H-NMR (300 MHz, CDCl₃): δ 1.44 (s, 9H), 2.80 (t, 2H, J = 6.32 Hz), 3.06 (t, 2H, J = 6.73 Hz), 3.44 (q, 2H), 4.70 (t, 2H, J = 7.62 Hz), 4.87 (br s, 1H). MS (EI)⁺ m/z: 299 [M+H]⁺.

The above linker intermediate was also prepared by the following method: TEA (3.56 g, 35.2 mmol) was added to a solution of cysteamine hydrochloride (2g, 17.60 mmol) and **LI-3b** (4.29g, 17.6mmol) in methanol (25mL) at 0 °C and stirred at RT for 4 h. To the mixture, which contained the intermediate free amine (**LI-5**), a solution of (BOC)₂O (7.68 g, 35.2 mmol) and TEA (3.56 g, 35.2 mmol) in MeOH (10mL) was added and the mixture was stirred overnight. The reaction mixture was filtered through celite

and evaporated to dryness. The residue was purified by column chromatography to afford 0.380 g (7 %) of LI-2f.

Example 10

Synthesis of 2-((2-Aminoethyl)dithio)ethyl nitrate.TFA salt (**LI-5.TFA**): To an ice- cold solution of **LI-2f** (2 g, 6.7 mmol) in DCM (20 mL) was added TFA (5 mL) and stirred at room temperature for 1 h. The mixture was concentrated, the residue was triturated with ether and concentrated to remove traces of TFA and finally dried to afford LI-5.TFA, which was used as such in further reactions.

The above linker intermediate **LI-5.TFA** was also synthesized as described below: TEA (3.56 g, 35.2mmol) was added drop-wise to a solution of cysteamine hydrochloride (2g, 17.60mmol) and **LI-3b** (4.29g, 17.6mmol) in MeOH (25mL) at 0 °C and stirred at RT for 4 h. The mixture was cooled to 0 °C and a solution of (Boc)₂O (7.68 g, 35.2mmol) in MeOH (10 mL) was added, followed by TEA (3.56 g, 35.2mmol), and stirred overnight at RT. The reaction mixture was filtered through celite and the filtrate concentrated. The residue was purified by column chromatography to afford 0.38 g (7.25%) of LI-2f, which was identical (TLC and ¹H-NMR) to that obtained in Example 9. Removal of the Boc group from **LI-2f** to give **LI-5.TFA** was accomplished as described in Example 10.

Example 11

Synthesis of methyl r(2-hydroxyethyl)dithiolacetate (**L3I2a**): Methyl mercaptoacetate (10.32 g, 97.4 mmol) was added to a solution of SL-I (10.0 g, 64.93 mmol) in DCM (150 mL) at RT, followed by TEA (18 mL, 129 mmol) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 2.7 g (22.9 %) of **L3I2a** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.95 (t, 2H, J = 2.5 Hz), 3.49 (s, 2H), 3.76 (s, 3H), 3.86 (q, 2H, J = 5.64). MS (m/z): 182 [M+H]⁺.

Example 12

Synthesis of prodrug **I-C1-PD10**: This prodrug was synthesized as described in Scheme 11, Method B. Thus, TEA (0.73 mL, 10 mmol) was added to a suspension of cetirizine dihydrochloride (2.0 g, 4.68 mmol) in DCM (50 mL), followed by a solution of SL-I (0.72 g, 4.67 mmol), DCC (1.13 g, 5.47 mmol) and DMAP (0.112g, 1 mmol) and stirred at RT for 15 h. The mixture was concentrated and the residue, after usual aqueous work-

up and chromatographic purification, gave 0.44 g (19%) of **I-C1-PD10**. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.50 (bs, 4H), 2.80 (bs, 6H), 2.87 (t, 2H, $J = 6.09$ Hz), 2.94 (t, 2H, $J = 7.32$ Hz), 3.75 (m, 2H), 3.86 (t, 2H, $J = 6.12$ Hz), 4.13 (s, 2H), 4.24 (s, 1H), 4.40 (t, 2H, $J = 6.09$ Hz) and 7.22-7.35 (m, 9H). MS (m/z): 527 $[\text{M}+\text{H}]^+$.

5 Example 13

Synthesis of prodrug **I-C1-PD6**: Step 1: To a suspension of aspirin (3 g, 16.65 mmol) in benzene (25 mL) and DMF (2 drops) at 0-5 $^{\circ}\text{C}$ was added oxalyl chloride (1.7 mL, 19.98 mmol) in benzene (5 mL). The reaction mixture was refluxed at 85 $^{\circ}\text{C}$ for 2 h, cooled to RT and concentrated to give a yellow oil.

10 Step 2: The yellow oil was dissolved in benzene (30 mL), silver cyanate (2.99 g, 19.98 mmol) was added and the mixture was refluxed for 1h in the dark.

Step 3: The reaction mixture was cooled to RT, and a solution of **SL-I** (2.56 g, 16.65 mmol) in benzene (5 mL). The reaction mixture was stirred for 1h, filtered through celite, concentrated and purified by column chromatography to afford 2.24 g (54%) of **I-C1-**

15 **PD6**. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 2.12 (s, 3H), 2.83-2.91 (m, 4H), 3.84 (t, $J = 5.9$ Hz, 2H), 4.27 (t, $J = 5.16$ Hz, 2H), 6.20 (br s, 1H), 7.06 (d, $J = 8.21$ Hz, 1H), 7.19 (t, $J = 7.55$ Hz, 1H), 7.59 (t, $J = 7.24$ Hz, 1H), 7.97 (d, $J = 6.82$ Hz, 1H). MS: m/z 360.06 $[\text{M}+\text{H}]^+$, 377.05 $[\text{M}+\text{NH}_4]^+$, 382.01 $[\text{M}+\text{Naf}]$, 357.96 $[\text{M}-\text{H}]^-$.

Example 14

20 Synthesis of prodrug **I-C1-PD11**: To a solution of **SL-I** (7g, 45.45 mmol) and valproic acid (7.85 g, 54.5 mmol) in DCM (80 mL) was added DCC (11.26 g, 54.5 mmol), followed by DMAP (6.65 g, 54.5 mmol), and the resulting suspension was stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 2.82 g (22 %) of **I-C1-PD11** were obtained as a colorless oil. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 0.86-0.93 (m, 6H), 1.22-1.29 (m, 8H), 1.32-1.59 (m, 4H), 2.37 (m, 1H), 3.89 (t, 2H, $J = 5.7$ Hz), 4.35 (t, 2H, $J = 6.5$ Hz).

Example 15

Synthesis of prodrug **I-C1-PD13**: To a solution of valpromide (5 g, 34.9 mmol) in DCE (50 mL) was added oxalyl chloride (3.7 mL, 41.88 mmol) at 0 $^{\circ}\text{C}$ and refluxed for 16 h.

30 The mixture was added to a solution of **SL-I** (10.76 g, 69.8 mmol) in DCE (80 mL) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification,

5.01 g (44%) of **I-C1-PD13** were obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.21 Hz), 1.23-1.66 (m, 9H), 2.90 (t, 2H, J = 6.46 Hz), 2.97 (t, 2H, J = 5.82 Hz), 3.90 (t, 2H, J = 5.82 Hz), 4.44 (t, 2H, J = 6.48 Hz), 7.61 (br s, 1H)

Example 16

5 Synthesis of prodrug **I-C1-PD14**: To a cold solution of diphosgene (0.9 mL, 7.14 mmol) in DCM (5 mL) was added a solution of **I-C1-PD11** (1 g, 3.57 mmol) and DIPEA (1.9 mL, 10.71 mmol) in DCM (5 mL). The reaction mixture was stirred at RT for 30 min. DCM and excess phosgene were removed under vacuum and the resulting solid was dissolved in DCM (5 mL). To it was added a suspension of methanesulfonamide (0.41 g, 4.284 mmol) and DIPEA (1.9 mL, 10.71 mmol) in DCM (5 mL) at 0-5 °C and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 1.1 g (77%) of **I-C1-PD14** were obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.22 Hz), 1.27-1.63 (m, 8H), 2.34-2.43 (m, 1H), 2.90 (t, 2H, J = 7.0 Hz), 2.96 (t, 2H, J = 6.13 Hz), 3.30 (s, 3H), 4.36 (t, 2H, J = 6.98 Hz), 4.45 (t, 2H, J = 6.14 Hz). MS: (ES⁺) m/z 402 [M+H]⁺, 419 [M+NH₄]⁺, 424 [M+Na]⁺, 440 [M+K]⁺; (ES⁻) 401 [M-H]⁻.

10

15

Example 17

Synthesis of prodrug **I-A1-PD1**:

This prodrug was synthesized as shown in Scheme 14, Method B. Thus, to a solution of amlodipine (18.75 g, 45.86 mmol) in DCM (100 mL) at 0 °C was added triphosgene (4.62 g, 15.59 mmol) followed by TEA (7.71 g, 76.35 mmol) in DCM (10 mL) and stirred at RT for 3 h. To this was added a solution of **LI-Ia** (9.0 g, 48.86 mmol) and TEA (4.63 g, 45.86 mmol) in DCM (10 mL) at 0 °C and stirred at RT for 3 d. The mixture was concentrated and the residue purified by column chromatography to yield 23 g (79.5%) of **I-A1-PD1**. ¹H-NMR (300 MHz, CDCl₃): δ 1.16 (t, 3H, J = 7.5 Hz), 2.05 (s, 3H), 2.34 (s, 3H), 2.86-2.94 (m, 4H), 3.43-3.45 (m, 2H), 3.59-3.62 (m, 5H), 4.0-4.35 (m, 4H), 4.30-4.35 (m, 4H), 4.69 (q, 2H, J = 15 Hz), 5.20 (bs, 1H), 5.38 (s, 1H), 7.01-7.34 (m, 4H). MS (m/z): 631 [M+H]⁺, 653 [M+Na]⁺.

20

25

Example 18

30 Synthesis of prodrug **I-A1-PD2**: To a solution of **I-A1-PD1** (23.0 g, 36.45 mmol) in MeOH (250 mL) at 0 °C was added a solution of K₂CO₃ (7.54 g, 54.67 mmol) in water

(55 mL) and stirred for 10 min. The mixture was concentrated and purified by column chromatography to afford 18 g (83.8%) of the intermediate **I-A1-PD2**. ¹H-NMR (300 MHz, CDCl₃): δ 1.16 (t, 3H, J = 6 Hz), 2.35 (s, 3H), 2.84-2.88 (t, 2H, J = 6 Hz), 2.90-2.94 (t, 2H, J = 6 Hz), 3.44 (bs, 2H), 3.59-3.61 (bs, 5H), 3.84-3.91 (m, 2H), 4.0-4.03 (q, 2H, J = 3.11 Hz), 4.33 (bs, 2H), 4.69 (q, 2H, J = 15 Hz), 5.28 (bs, 1H), 5.37 (s, 1H), 7.12-7.36 (m, 4H). MS (ES⁺): m/z 589 [M⁺], 611 [M+Na]⁺.

Example 19

Synthesis of prodrug **I-A1-PD3**: To a suspension of lamotrigine (13.09 g, 51.02 mmol) in toluene (100 mL) at 110 °C was added a solution of **LI-lxy** (synthesized from **LI-Ia** and CDI, as described in Scheme 10) (16.27 g, 56.12 mmol) in THF (50 mL) and stirred at 110 °C overnight. The reaction mixture was purified by column chromatography to give 6.0 g (24%) of **I-A1-PD3** as a white solid. ¹H NMR (CD₃OD, 300 MHz) δ 2.04, (s, 3H), 2.96-3.02 (m, 4H), 4.30-4.35 (m, 2H), 4.45 (t, 2H), 7.38-7.45 (m, 2H), 7.67-7.69 (m, 1H). MS: (ES⁺) m/z 477.9 (M+H)⁺, 499.9 (M+Na)⁺.

Example 20

Synthesis of prodrug **I-A1-PD4**: To a solution of **I-A1-PD3** (2 g, 4.18 mmol) in MeOH (15 mL) and THF (5 mL) at 0 °C was added a solution of K₂CO₃ (0.886 g, 6.276 mmol) in water (5 mL) and stirred at 0 °C for 3 h. After usual aqueous work-up and chromatographic purification, 1.1 g (60%) of **I-A1-PD4** were obtained as a white solid. ¹H NMR (DMSO d₆, 300 MHz): δ 2.75-2.82 (m, 2H), 2.96-3.0 (m, 2H), 3.0 (s, 1H), 3.6 (t, 2H, J = 6.3 Hz), 4.30 (t, 2H, J = 6.6 Hz), 7.38-7.49 (m, 2H), 7.72-7.75 (m, 1H). MS: (ES⁺) m/z 436 (M+H)⁺, 457 (M+Na)⁺.

Example 21

Synthesis of prodrug **I-A1-PD5**: To a solution of diphosgene (0.99 mL, 8.24 mmol) in DCM (3 mL) at 0 °C was added a solution of **L3I2a** (0.5 g, 2.74 mmol) and Hunig's base (2.39 mL, 13.73 mmol) in DCM (3 mL). The mixture was stirred at 0 °C for 30 min and concentrated to yield the intermediate **L3I3a** as a light-yellow semi-solid. A solution of a mixture of gabapentin ethyl ester hydrochloride (0.77g, 3.29 mmol) and Hunig's base (1.7 mL, 9.79 mmol) in DCM (6 mL) was added to the intermediate **L3I3a** at RT and stirred for 15 h. After usual aqueous work-up and chromatographic purification, 0.34 g (30 %) of **I-A1-PD5** were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.26

(t, 3H, J = 6 Hz), 1.22-1.51 (m, 10 H), 2.26 (s, 2H), 2.96 (t, 2H, J = 6 Hz), 3.18 (d, 2H, J = 6 Hz), 3.49 (s, 2H), 3.82 (s, 3H), 4.09 (q, 2H, J = 6 Hz), 4.29 (t, 2H, J = 6 Hz), 5.39 (bs, 1H). MS: (ES⁺) m/z 408 (M+H)⁺, 430 (M+Na)⁺; (ES⁻) m/z 406 (M-H)⁻.

Example 22

- 5 Synthesis of prodrug **I-A1-PD6**: To a solution of **I-A1-PD8** (1.0 g, 2.63 mmol) in DCM (3 mL) at RT was added CDI (0.46 g, 2.89 mmol) and stirred for 15 h. A suspension of serine methyl ester hydrochloride (0.61 g, 3.95 mmol) in DCM (4 mL) and TEA (1.1 mL, 7.90 mmol) was added and stirring continued for 15 h. After usual aqueous work-up and chromatographic purification, 0.706 g (51%) of **I-A1-PD6** were obtained as a colorless
- 10 oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.1 Hz), 1.35-1.51 (m, 10H), 2.28(s, 2H), 2.91-2.98 (m, 4H), 3.16 (d, 2H, J = 9Hz), 3.78 (s, 3H), 3.94-4.38 (m, 9H), 5.5 (bs, 1H), 6.0 (bs, 1H). MS: (ES)⁺: m/z 525 (M+H)⁺, 547 (M+Na)⁺. (ES)⁻: m/z 523 (M-H)⁺.

Example 23

- Synthesis of prodrug **I-A1-PD7**: To a solution of **I-A1-PD8** (86 mg, 0.22 mmol) in
- 15 DCM (9 mL) at RT was added CDI (40 mg, 0.24 mmol) and stirred for 15 h, after which a solution of dimethyl glutamate (80 mg, 0.45 mmol) and TEA (0.06 mL, 0.45 mmol) was added and stirred for 2 d. After usual aqueous work-up and chromatographic purification, 97 mg (74 %) of **I-A1-PD7** were obtained as a colourless oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J=7.13 Hz), 1.36-2.5 (m, 16H), 2.93(t, 4H, J = 6.46
- 20 Hz), 3.19 (d, 2H, J = 6.67), 3.67 (s, 3H), 3.74 (s, 3H), 4.12 (q, 2H, J = 7.13 Hz), 4.25-4.44 (m, 5H), 5.4 (bs, 1H), 5.65 (bs, 1H). MS: (ES⁺) m/z 581 (M+H)⁺, 603 (M+Na)⁺; (ES⁻) m/z 571 (M-H)⁻.

Example 24

- Synthesis of prodrug **I-A1-PD9**: To a suspension of gabapentin (10 g, 58.4 mmol) in
- 25 THF (100 mL) at 0 °C was added IN NaOH (70 mL), followed by (Boc)₂O. The mixture was stirred at RT for 15 h. After washing with diethyl ether (100 mL x 2), the aqueous layer was acidified with solid KHSO₄ and extracted with EtOAc (100 mL x 2). Organic extracts were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to afford 10.41g (68 %) of boc-protected gabapentin as a white solid.
- 30 A mixture of boc-protected gabapentin (5.0 g, 18.45 mmol) and CDI (3.59 g, 22.14 mmol) in DCM (75 mL) was stirred for 15 h. The mixture was concentrated and

dissolved in acetonitrile (50 mL), followed by the addition of 30 % aqueous solution of ammonia (50 mL) and stirred for 1.5 h at RT. After usual aqueous work-up, 4.5 g (90 %) of boc-protected gabapentin-amide were obtained as a white solid.

To a solution of boc-protected gabapentin-amide (2.59 g, 9.61 mmol) in DCM (12 mL) at 0 °C was added solution of TFA (4mL) in DCM (4 mL) and stirred for 2.5 h at RT. The mixture was concentrated and dissolved in DCM (20 mL). This was treated successively with Hunig's base (6.7 mL, 38.46 mmol) and **LI-Ia** (1.45g, 7.39 mmol), and stirred at RT for 3 h. After usual aqueous work-up and chromatographic purification, 1.19 g (41 %) of **I-A1-PD9** were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.28-1.48 (m, 10H), 2.06 (s, 3H), 2.15 (s, 2H), 2.91 (t, 4H, J = 6.0 Hz), 3.23 (d, 2H, J = 6.0 Hz), 4.28-4.38(m, 4H), 5.7(bs, 1H). MS: (ES)⁺ m/z 393(M+H)⁺; (ES)⁻ m/z 392(M-H)⁻.

Example 25

Synthesis of prodrug **I-A1-PD10** : A mixture of **I-A1-PD8** (1.0g, 2.63 mmol) and CDI (0.469 g, 2.89 mmol) in DMF (3 mL) was stirred for 12 h, after which N,N'-dimethylethylenediamine (0.56mL, 5.26 mmol) and DMAP (0.32 g, 2.63 mmol) was added. The mixture was stirred for 4 h. After usual aqueous work-up and chromatographic purification, 0.763 g (59 %) of were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 6.0 Hz), 1.28-1.53 (m, 10H), 2.24 (s, 6H), 2.29 (s, 2H), 2.42 (t, 2H, J = 6.0 Hz), 2.92 (t, 4H, J = 6.0 Hz), 3.20(d, 2H, J = 6.0 Hz), 3.26 (q, 4H, J = 6.0 Hz), 4.13 (q, 2H, J = 7.0 Hz), 4.31 (t, 4H, J = 6.0Hz), 7.26 (bs, 1H). MS: (ES)⁺ m/z 494 (M+H)⁺, 516 (M+Na)⁺; (ES)⁻ m/z 492 (M-H)⁻.

Example 26

Synthesis of prodrug **I-A1-PD11**: A mixture of **LI-Ia** (2.0 g, 10.20 mmol) and CDI (1.98 g, 12.24 mmol) in DCM (12 mL) was stirred for 2 h and concentrated. The residue was dissolved in acetonitrile, and a suspension of gabapentin (2.62 g, 15.30 mmol) in saturated NaHCO₃ (15 mL) was added. The mixture was stirred at RT for 15 h. Acetonitrile was removed by distillation and the basic aqueous portion was washed with diethyl ether (100 mL x 2). The aqueous layer was acidified using 2N HCl and extracted in EtOAc (60 mL x 3). The organic layer was concentrated and the residue was purified by chromatographic purification, 1.76 g (43 %) of **I-A1-PD11** were obtained as a

colorless oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.27-1.68 (m, 10H), 2.07 (s, 3H), 2.31 (s, 2H), 2.92 (t, 4H, $J = 6.0$ Hz), 3.22 (d, 2H, $J = 9.0$ Hz), 4.31-4.35 (m, 4H), 5.43 (bs, 1H). MS: (ES) $^+$ m/z 392 (M-H) $^+$.

Example 27

- 5 Synthesis of prodrug **I-A1-PD13**: This prodrug was synthesized as shown in Scheme 12, Method B. Thus, to a solution of diphosgene (7.02 mL, 58.18 mmol) in DCM (20 mL) at 0 $^\circ\text{C}$ was added a solution of **LI-Ia** (5.71 g, 29.09 mmol) and Hünig's base (25.3 mL, 145.45 mmol) in DCM (30 mL) and stirred at RT for 40 min. The mixture was concentrated and a mixture of gabapentin ethyl ester hydrochloride (7.546 g, 32 mmol)
- 10 and Hünig's base (11.15 mL, 64 mmol) in DCM (50 mL) was added and stirred overnight. Reaction mixture was concentrated and, after usual aqueous work-up and column chromatography, 8.42 g (67 %) of **I-A1-PD13** were obtained. ^1H NMR (CDCl_3 , 300 MHz): δ 1.22 (t, 3H, $J = 7.3$ Hz), 1.27-1.68 (m, 10H), 2.06 (s, 3H), 2.27 (s, 2H), 2.91 (t, 4H, $J = 6.6$ Hz), 3.19 (d, 2H, $J = 6.7$ Hz), 4.08 - 4.15 (q, 2H, $J = 7.1$ Hz), 4.27-4.34 (q,
- 15 4H, $J = 6.4$ Hz), 5.4 (bs, 1H). MS: m/z 422 $[\text{M}+\text{H}]^+$, 444 $[\text{M}+\text{Naf}]^+$.

Example 28

- Synthesis of prodrug **I-A1-PD8**: To an ice-cold solution of **I-A1-PD13** (8.0 g, 18.98 mmol) in MeOH (30 mL) was added a solution of K_2CO_3 (5.24 g, 37.96 mmol) in water (38 mL). After 15 min, the mixture was concentrated. After usual aqueous work-up, 5.0
- 20 g (69 %) of **I-A1-PD8** were obtained. ^1H NMR (CDCl_3 , 300 MHz): δ 1.25 (t, 3H, $J = 7.11$ Hz), 1.30-1.71 (m, 10H), 2.87-2.94 (m, 4H), 2.27 (s, 2H), 3.18 (d, 2H, $J = 6.6$ Hz), 3.87 (t, 2H, $J = 5.7$ Hz), 4.09-4.16 (q, 2H, $J = 7.12$ Hz), 4.31 (t, 2H, $J = 6.51$ Hz), 5.44 (bs, 1H). MS: m/z 380 $[\text{M}+\text{H}]^+$, 402 $[\text{M}+\text{Na}]^+$.

Example 29

- 25 Synthesis of prodrug **I-A1-PD12**: To a solution of diphosgene (1.91 mL, 15.81 mmol) in DCM (20 mL) at 0 $^\circ\text{C}$ was added a solution of **I-A1-PD8** (4 g, 10.54 mmol) and Hünig's base (5.5 mL, 31.62 mmol) in DCM (30 mL). The mixture was stirred at RT for 40 min, cooled to 0-5 $^\circ\text{C}$, and dry ammonia gas was passed through it for 30 min. Reaction mixture was concentrated and, after usual aqueous work-up, 5.3 g (91 %) of **I-A1-PD12**
- 30 were obtained. ^1H NMR (CDCl_3 , 300 MHz): δ 1.23 (t, 3H, $J = 7.1$ Hz), 1.27-1.79 (m,

10H), 2.28 (s, 2H), 2.91-3.03 (m, 4H), 3.19 (d, 2H, J = 6.7 Hz), 4.12 (q, 2H, J = 7.1 Hz), 4.31 (t, 4H, J = 6.4 Hz), 5.4 (t, 1H, J = 6.0 Hz). MS: m/z 423 [M+H]⁺, 446 [M+Na]⁺.

Example 30

Synthesis of prodrug **I-A1-PD14**: Ethyl chloroformate (0.86 g, 7.9 mmol) was added to a solution of S-carbamoylmethyl-S-methylhexanoic acid (M. S. Hoekstra *et al.*, *Org. Proc. Res. Dev.* 1997, 1, 26-38) (1.0 g, 5.3 mmol) in THF (6 mL) at -10 °C, followed by TEA (2.4 mL, 17.0 mmol) and the mixture was stirred at -10 °C for 30 min. A solution of NaN₃ (1.73 g, 26.6 mmol) in water (10 mL) was added and stirred for 2 h at -10 °C. The reaction mixture was brought to RT and extracted with EtOAc (3 x 25 mL), washed with water (2 x 25 mL), dried over Na₂SO₄ and concentrated. Toluene (20 mL) was added to the residue and refluxed for 6 h. After cooling to RT, a solution of and SL-I (825 mg, 5.3 mmol) in DCM (10 mL) was added and stirred at RT for 14 h. After usual aqueous work-up and chromatographic purification, 318 mg (17 %) of **I-A1-PD14** were obtained as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 0.89-0.95 (m, 6H), 1.25-1.29 (m, 2H), 1.62-1.71 (m, 1H), 2.04-2.1 (m, 1H), 2.38 (d, J = 5.2 Hz, 2H), 2.87-2.95 (m, 4H), 3.05-3.36 (m, 2H), 3.88 (t, J = 5.7 Hz, 2H), 4.34 (t, J = 6.2 Hz, 2H), 5.06 (br s, 1H). MS: m/z 338 [M]⁺.

Example 31

Synthesis of prodrug **I-A1-PD15Ba**: To a solution of **I-A1-PD4** (0.350 g, 0.802 mmol) in DMF (3 mL) at RT was added CDI (0.195g, 1.204 mmol) and stirred at RT for 3 h. This mixture was added to a suspension of methanesulphonamide (0.304 g, 3.2 mmol) in DMF (4 mL) and NaH (0.153 g, 3.2 mmol) at 0 °C and stirred at RT for 4 h. The reaction was quenched with ice and, after usual aqueous work-up and chromatographic purification, 0.12 g (26%) of **I-A1-PD15Ba** were obtained as a white solid. ¹H NMR (CDCl₃ + CD₃OD, 300MHz): δ 2.83- 2.90 (m, 4H), 3.10 (s, 3H), 4.26-4.36 (m, 4H), 7.19-7.28 (m, 2H), 7.48-7.51 (m, 1H). MS: (ES⁺) m/e 556.96 (M+H)⁺, 578.92 (M +Na)⁺.

Example 32

Synthesis of prodrug **I-A1-PD16**: CDI (4 g, 24.7 mmol) was added to a solution of LI-2c (4 g, 15.8 mmol) in THF (30 mL) and stirred at RT for 2 h. Then, a solution of gabapentin (4 g, 23.4 mmol) in 20 % NaHCO₃ solution (10 mL) was added and stirred overnight at RT. The reaction mixture was neutralized with 0.5N HCl (pH ~ 4), extracted

with EtOAc (4 x 40 mL), dried over Na₂SO₄, concentrated and purified by column chromatography to afford 4.7 g (66 %) of **I-S12-PD2** as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.45-1.49 (br s, 19H), 2.35 (s, 2H), 2.80-2.97 (m, 4H), 3.24 (d, J = 5.7 Hz, 2H), 3.46 (m, 2H) 4.33 (t, J = 5.7 Hz, 2H), 5.0 (br s, 1H), 5.71 (br s, 1H). MS: (m/z) [ES]⁻ 449.1 [M-H]⁺; [ES]⁺ 451.2 [M+H]⁺.

EtOAc saturated with HCl gas (5mL) was added to **I-S12-PD2** (0.55 g, 1.22 mmol) and stirred at RT for 10 h. Solvent was removed under reduced pressure and purified by preparative HPLC to give 425 mg (90 %) of **I-A1-PD16** as a colorless liquid. ¹H NMR (300 MHz, CD₃OD): δ 1.52 (br s, 10H), 2.4 (s, 2H), 2.98-3.09 (m, 4H), 3.27-3.34 (m, 2H), 3.61 (s, 2H), 4.5 (t, J = 6.0 Hz, 2H). MS: [ES]⁺ m/z 351.0 [M+H]⁺.

Example 33

Synthesis of prodrug **I-A2-PD1**: To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (20 mL) and DCM (4 mL) was added oxalyl chloride (0.61 mL, 7.05 mmol), and heated at 70 °C for 8h. Reaction mixture was cooled and added to a solution of SL-I (1.81 g, 11.75 mmol) in DCM (15 mL) and stirred at RT overnight. After chromatographic purification, 1.13 g (41%) of **I-A2-PD1** were obtained. ¹H NMR (CDCl₃, 300 MHz): δ (ppm): 0.87 (t, J = 7.3 Hz, 3H), 1.84-2.04 (m, 4H), 2.41 (t, J = 6.9 Hz, 2H), 2.69 (bs, 1H), 2.87-2.95 (m, 4H), 3.02-3.11 (m, 1H), 3.65-3.75 (m, 1H), 3.85-3.95 (m, 2H), 4.06-4.12 (m, 1H), 4.34-4.41 (m, 2H), 8.69 (bs, 1H). MS: (ES⁺): m/z 351.0 [M+H]⁺; 372.9 [M+Na]⁺.

Example 34

Synthesis of prodrug **I-A3-PD1**: To a solution of **I-S13-PD1** (which was synthesized as described in Example 37, Step 2) (215 mg, 0.292 mmol) and triisopropylsilane (60 μL) in 0.75 mL of DCM was added 20 % TFA in DCM (0.5 mL) and stirred at RT for 90 min. The mixture was concentrated and the residue purified by column chromatography to give 65 mg (46%) of **I-A3-PD1**. ¹H-NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.85-2.92 (m, 4H), 3.87 (t, 2H, J = 4.5 Hz), 4.37 (t, 2H, J = 6.0 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J = 3.0 Hz). MS (m/z): 493 [M-H]⁻, 517 [M+Naf].

Example 35

Synthesis of prodrugs **I-A3-PD3a** and **I-A3-PD3b**: Step 1: DSC (210 mg, 0.824 mmol) and TEA (0.230 mL, 1.64 mmol) were added to a solution of methyl [(2-

hydroxyethyl)dithio]acetate (100mg, 0.549 mmol) in acetonitrile (1 mL) at 0 °C and stirred at RT for 3h. The mixture was concentrated and the residue dissolved DCM. Usual aqueous work-up and chromatographic purification gave the crude intermediate.

Step 2: TEA (24mg, 0.236 mmol) and DMAP (13 mg) were added to a mixture of valdecoxib (62mg, 0.195 mmol) and the product obtained from step 1 above in THF (1 mL) and stirred at RT for 3 d. The mixture was concentrated and the residue dissolved in EtOAc. After usual aqueous work-up and chromatographic purification, 53 mg (52%) of **I-A3-PD3a** obtained. ¹H- NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.97 (t, 2H, J = 6.0 Hz), 3.48 (s, 2H), 3.76 (s, 3H), 4.37 (t, 2H, J = 6.0 Hz), 7.33-7.40 (m, 7H), 8.03-8.12 (m, 2H). MS (m/z): 521 [M-H]⁻.

Step 3: The above material was converted to the corresponding mono-, and/or di-sodium salt forms **I-A3-PD3b** by using standard methods. Thus, to a cold solution of the above compound (150 mg, 0.287 mmol) in THF (1 mL) was added 1M LiOH solution (28 mg in 1mL water) and stirred overnight at RT. The mixture was concentrated, the residue diluted with water, acidified with 1N HCl (~3 ml, pH ~3) and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 20 mg (13%) of product were obtained. ¹H- NMR (300 MHz, CDCl₃): δ 2.49 (s, 3H), 2.70-2.89 (m, 4H), 4.23-4.33 (m, 2H), 7.28-7.38 (m, 7H), 8.01-8.03 (m, 2H).

Example 36

Synthesis of prodrug **I-A3-PD4**: This prodrug was synthesized as described in Scheme 13, Method B.

Step 1: Synthesis of intermediate **LI-8**:

CDI (1.65 g, 10.19 mmol) was added to a solution of **LI-Ia** (2.0 g, 10.19 mmol) in DMF (10 mL) and stirred at RT for 3 h. N,N-Dimethylethylenediamine (1.2 mL, 11.12 mmol) was added and stirred for 2 h. The mixture was concentrated and the residue taken up in EtOAc. After usual aqueous work-up and chromatographic purification, 1.3 g (41%) **LI-8** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.07 (s, 3H), 2.31 (bs, 6H), 2.51 (t, 2H, J = 6.0 Hz), 2.91 (t, 4H, J = 6.0 Hz), 3.31 (q, 2H, J = 6.0 Hz), 4.28-4.34 (m, 4H), 5.52 (bs, 1H). MS (m/z): 333 [M+Na]⁺.

Step 2: Synthesis of intermediate **LI-9**: To a solution of **LI-8** (1.3 g, 4.18 mmol) in MeOH (7 mL) was added a 1.25M solution of K₂CO₃ (5 mL) and stirred at RT for 1h.

The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up, 1.02 g (91%) of product were obtained. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.29 (s, 6H), 2.54 (t, 2H, $J = 6.0$ Hz), 2.86-2.99 (m, 4H), 3.33 (q, 2H, $J = 5.0$ Hz), 3.86 (t, 2H, $J = 6.0$ Hz), 4.31 (t, 2H, $J = 6.0$ Hz), 5.71 (bs, 1H). MS (m/z): 269 $[\text{M}+\text{H}]^+$. This product was

5 used as such in the next step.

Step 3: Synthesis of intermediate LI-10: A solution of LI-9 (1.02 g, 3.80 mmol) in acetonitrile (10 mL) was added to a cold solution of DSC (1.46 g, 5.70 mmol) in acetonitrile (50 mL) followed by TEA (1.58 mL, 11.40 mmol), and stirred overnight at RT. The mixture was concentrated and the residue was taken up in DCM. After usual

10 aqueous work-up, 1.33 g (85%) of LI-10 were obtained.

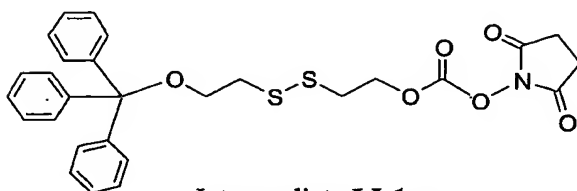
Step 4: Synthesis of I-A3-PD4: TEA (0.194 mL, 1.39 mmol) and DMAP (73 mg, 0.6 mmol) were added to a solution of LI-10 (1.33 g, 3.24 mmol) and valdecocix (364 mg, 1.16 mmol) in THF (6 mL) and stirred at RT for 5 d. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up and chromatographic

15 purification, 177 mg (12 %) of LI-10 were obtained. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.46 (s, 3H), 2.85-2.95 (m, 10H), 3.28 (t, 2H, $J = 6.0$ Hz), 3.65 (q, 2H, $J = 3.0$ Hz), 4.22-4.28 (m, 4H), 7.22-7.41 (m, 7H), 7.94 (d, 2H, $J = 9.0$ Hz). MS (m/z): 609 $[\text{M}+\text{H}]^+$. This product was converted to water-soluble hydrochloride salt form using standard methods.

Example 37

20 Synthesis of prodrug I-A3-PD5: This prodrug was synthesized as shown in Scheme 13, Method B.

Step 1: Synthesis of prodrug intermediate LI-1xy:



Intermediate LI-1xy

25

A solution of **LI-Ic** (1.0 g, 2.52 mmol) in acetonitrile (10 mL) was added to a solution of **DSC** (0.96 g, 3.78 mmol) in acetonitrile (20 mL) and stirred for 10 min. After cooling to 0 °C, **TEA** (1 ml, 7.57 mmol) was added and stirred at RT for 3.5 h. The solution was concentrated and the residue was taken up in DCM. After usual aqueous work-up, the crude product obtained was used as such in the next step.

Step 2: Synthesis of prodrug intermediate **I-S13-PD1**: A mixture of valdecoxib (280 mg, 0.892 mmol), **DMAP** (56 mg, 0.5 mmol) and **TEA** (150 µL, 1.06 mmol) in **THF** (5 mL) was stirred at RT for 4.5 d. The mixture was concentrated and the residue dissolved in **EtOAc**. After usual aqueous work-up and chromatographic purification, 354 mg (54 %) of **I-S13-PD1** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.47 (s, 3H), 3.32-3.41 (m, 4H), 4.28 (t, 2H, J = 6.0 Hz), 4.47 (t, 2H, J = 6.0 Hz), 7.20-7.61 (m, 22H), 8.00 (d, 2H, J = 9.0 Hz). MS (m/z): 736 [M-H]⁻.

Step 3: Synthesis of intermediate **I-A3-PD1**: To a solution of **I-S13-PD1** (215 mg, 0.292 mmol) and triisopropylsilane (60 µL) in 0.75 ml of DCM was added 20%TFA in DCM (0.5 mL) and stirred at RT for 90 min. The mixture was concentrated and the residue purified by column chromatography to give 65 mg (46%) of **I-A3-PD1**. ¹H-NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.85-2.92 (m, 4H), 3.87 (t, 2H, J = 4.5 Hz), 4.37 (t, 2H, J = 4.5 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J = 3.0 Hz). MS (m/z): 493 [M-H]⁻, 517 [M+Na]⁺.

Step 4: Synthesis of **I-A3-PD5-Me-ester**: **CDI** (40mg, 0.243 mmol) was added to a solution of **I-A3-PD1** (100mg, 0.202 mmol) in **DMF** (0.5 mL) and stirred at RT for 2.5 h. To this were added a solution of dimethyl glutamate (53 mg, 0.303 mmol) in **DMF** (0.3 mL) and **DMAP** (37 mg, 0.303 mmol) and stirred overnight at RT. The mixture was dissolved in **EtOAc** and, after usual aqueous work-up and chromatographic purification, 110 mg (78%) of **I-A3-PD5-Me-ester** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.71-1.91 (m, 2H), 2.38-2.42 (m, 2H), 2.44 (s, 3H), 2.84-2.95 (m, 4H), 3.66 (s, 3H), 3.67 (s, 3H), 4.31-4.34 (m, 4H), 4.43-4.52 (m, 1H), 7.31-7.41 (m, 7H), 8.02 (d, 2H, J = 9.0 Hz). MS (m/z): 694 [M-H]⁻.

Step 5: Synthesis of prodrug **I-A3-PD5**: **LiOH** (1.2 mL, 1.2 mmol) was added to a solution of **I-A3-PD5-Me-ester** (100 mg, 0.144 mmol) in **THF** (0.4 mL) at 0 °C and the mixture allowed to attain ambient temperature. After 30 min, the mixture was

concentrated and the residue diluted with water. Acidification with 1N HCl, followed by extraction with EtOAc, usual aqueous work-up and chromatographic purification gave 26 mg (26%) of **I-A3-PD5**. ¹H-NMR (300 MHz, CD₃OD): δ 1.82-1.97 (m, 1H), 2.05-2.13 (m, 1H), 2.30-2.40 (m, 2H), 2.48 (s, 3H), 2.84 - 2.94 (m, 4H), 4.06 - 4.08 (m, 1H), 4.15 - 4.22 (m, 4H), 7.30 (d, 2H, J = 9 Hz), 7.35 - 7.41 (m, 5H), 7.92 (d, 2H, J = 9.0 Hz). MS (nVz): 666 [M-H]⁻.

Example 38

Synthesis of prodrug **I-H1-PD1**: This prodrug was synthesized as shown in Scheme 14, Method B.

- 10 Step 1: A solution of metronidazole (5.0 g, 29.22 mmol) and CDI (5.21 g, 32.2 mmol) in DCM (100 mL) was stirred overnight at RT. After usual aqueous work-up, 7.32 g of the imidazolide of metronidazole were obtained, which was used as such in the next step.

- Step 2: A solution of the imidazolide of metronidazole (7.32 g) in DMF (30 mL) was added to a solution of **SL-I** (6.39 g, 41.43 mmol) in DMF (10 mL) and stirred at 60 °C
15 for 2.5 h. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up and chromatographic purification, 6.32 g (65%) of **I-H1-PD1** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.15 (bs, 1H), 2.52 (s, 3H), 2.83-2.92 (m, 4H), 3.84-3.92 (m, 2H), 4.34 (t, 2H, J = 6.0 Hz), 4.51 (t, 2H, J = 3.0 Hz), 4.53-4.62 (m, 2H), 7.96 (s, 1H).

20 Example 39

- Synthesis of **I-H1-PD14**: This prodrug was synthesized as described in Scheme 14, Method C. Thus, TEA (0.915 mL, 6.56 mmol) and DMAP (cat.) were added to a solution of LI-2C.TFA (541 mg, 3.94 mmol) and the imidazolide of metronidazole (synthesis described in Example 114) (870 mg, 3.28 mmol) in DMF (2 mL) and the
25 mixture was heated at 60 °C for 3.5 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 546 mg (48%) of **I-H1-PD14**. ¹H-NMR (300 MHz, CDCl₃): δ 2.48 (s, 3H), 2.76-2.96 (m, 4H), 3.46 (q, 2H, J = 6.0 Hz), 3.87 (t, 2H, J = 6.0 Hz), 4.41 (t, 2H, J = 6.0 Hz), 4.57 (t, 2H, J = 4.5 Hz), 7.90 (s, 1H). MS (m/z): 351[M+H]⁺.

30 Example 40

Synthesis of prodrug **I-H1-PD2**: This prodrug was synthesized as described in Scheme 14, Method C. Thus, CDI (180 mg, 1.1 mmol) was added to a solution of **I-H1-PD14** (350 mg, 1.0 mmol) in DMF (2 mL) and stirred at RT for 4 h. NJSI-Dimethylethylenediamine (88 mg, 1.0 mmol) was added and stirred for 3 h. The mixture
5 was concentrated and the residue purified by column chromatography to afford 175 mg (38%) of **I-H1-PD2**. ¹H-NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H), 2.49 (s, 6H), 2.51-2.55 (m, 2H), 2.81 (t, 2H, J = 6.0 Hz), 2.89 (t, 2H, J = 6.0 Hz), 3.27-3.33 (m, 2H), 3.46 (q, 2H, J = 6.0 Hz), 4.29 (t, 2H, J = 6.0 Hz), 4.40 (t, 2H, J = 4.5 Hz), 4.57 (t, 2H, J = 4.5 Hz), 5.55 (bs, 1H), 7.94 (s, 1H). MS (m/z): 465[M+H]⁺. This product was converted to water-
10 soluble hydrochloride salt form using a standard method.

Example 41

Synthesis of prodrug **I-H1-PD5**: This prodrug was synthesized as described in Scheme 14, Method A.

Step 1: Synthesis of Intermediate **I-S14-PD1**: A solution of the imidazolide of **LI-Ic** (1.6
15 g, 2.98 mmol) in acetonitrile (10 mL) was added to a solution of zidovudine (1.0 g, 3.74 mmol) in acetonitrile (20 mL) at RT, followed by DMAP (0.914 g, 7.48 mmol) and stirred for 24 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 1.62 g (79%) of intermediate **I-S14-PD1**. ¹H-NMR (300 MHz, CDCl₃): δ 1.95 (s, 3H), 2.35-2.45 (m, 2H), 2.78 (t, 2H, J = 6.6 Hz), 2.87
20 (t, 2H, J = 6.33 Hz), 3.38 (t, 2H, J = 6.33 Hz), 4.05 (m, 1H), 4.25 (m, 1H), 4.35 - 4.41 (m, 4H), 6.20 (t, 1H, J = 6.16), 7.21- 7.33 (m, 9H), 7.42-7.48 (m, 6H) and 8.49 (s, 1H). MS (m/z): 712 [M+ Na]⁺.

Step 2: Synthesis of **I-H1-PD5**: To a solution of **I-S14-PD1** in DCM (15 mL) were added triisopropylsilane (0.446 ml, 2.17 mmol), followed by 10% TFA in DCM (15 mL) and
25 stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography to afford 0.68 g (70%) of prodrug **I-H1-PD5**. ¹H-NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H), 2.30 (bs, 1H), 2.41-2.48 (m, 2H), 2.88 (t, 2H, J = 6.1 Hz), 2.96 (t, 2H, J = 6.6 Hz), 3.88 (t, 2H, J = 5.8 Hz), 4.05 (m, 1H), 4.29 (m, 1H), 4.30-4.48 (m, 4H), 6.18 (t, 1H, J = 6.3 Hz), 7.34 (s, 1H) and 9.11 (s, 1H). MS (m/z): 448 [M+H]⁺, 470
30 [M+Na]⁺.

Example 42

Synthesis of prodrug **I-S22-PD1**: This prodrug was synthesized in two steps as shown in Scheme 22.

Step 1: To a solution of diphosgene (0.35 mL, 2.93 mmol) in DCM (3mL) was added a
5 solution of **LI-Id** (0.404 mg, 1.75 mmol), Hunig's base (0.765 mL, 4.39 mmol) and the
resulting mixture was stirred at RT for 45 min. The mixture was concentrated, the residue
dissolved in DCM (5 mL), cooled in an ice-bath and treated with a solution of paclitaxel
(500 mg, 0.585 mmol), Hunig's base (0.765 mL, 4.39 mmol) and DMAP (cat.) in DCM
(5 mL) over 5 min and the resulting mixture was stirred at RT for 2 h. The mixture was
10 purified by column chromatography to give 519 mg (78%) of the protected intermediate
S22-I2 as an off-white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.28 (s, 3H),
1.68 (s, 3H), 2.04 (s, 3H), 2.23 (s, 3H), 2.37 - 2.45 (m, 2H), 2.46 (s, 3H), 2.50 - 2.52 (m,
2H), 2.90 - 2.95 (m, 4H), 3.82 (d, 1H, J = 7.0 Hz), 4.05 (s, 2H), 4.21 (d, 1H, J = 8.5 Hz),
4.32 (d, 1H, J = 8.0 Hz), 4.40 - 4.42 (m, 5H), 4.97 (d, 1H, J = 9.5 Hz), 5.29 (s, 1H), 5.43
15 (d, 1H, J = 2.5 Hz), 5.69 (d, 1H, J = 7.0 Hz), 6.00 (dd, 1H, J = 9.5 Hz, 2.5 Hz), 6.26-6.29
(m, 2H), 7.02 (d, 1H, J = 9.5 Hz), 7.38 - 7.61 (m, HH), 7.75 (d, 2H, J = 7.5 Hz), 8.15 (d,
2H, J = 7.5 Hz).

Step 2: To an ice-cold solution of **S22-I2** (60 mg, 0.0532 mmol) in MeOH (1 mL) was
added 2 drops of methanol saturated with ammonia gas and the resulting mixture was
20 stirred for 1 h. The reaction mixture was purified by column chromatography to give 38
mg (69%) of **I-S22-PD1** as an off white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s,
3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.23 (s, 3H), 2.38 - 2.42 (m, 2H), 2.46 (s,
3H), 2.50 - 2.58 (m, 2H), 2.84 (t, 2H, J = 5.4 Hz), 2.94 (t, 2H, J = 6.5 Hz), 3.82 (t, 3H, J =
6.0 Hz), 4.20 (d, 1H, J = 8.5 Hz), 4.31 (d, 1H, J = 8.5 Hz), 4.35 - 4.41 (m, 3H), 4.97 (d,
25 1H, J = 7.5 Hz), 5.44 (d, 1H, J = 2.5 Hz), 5.69 (d, 1H, 7.0 Hz), 6.0 (dd, 1H, J = 9.25 Hz,
2.25 Hz), 6.22-6.29 (m, 2H), 7.08 (d, 1H, J = 9.5 Hz), 7.36-7.60 (m, HH), 7.78 (d, 2H, J
= 7.5 Hz), 8.14 (d, 2H, J = 7.5 Hz).

Example 43

Synthesis of prodrug **I-S22-PD2**: To a solution of **I-S22-PD1** (38 mg, 0.0367 mmol) in
30 acetonitrile (0.6 mL) was added succinic anhydride (5 mg, 0.044 mmol) and DMAP
(cat.). The resulting mixture was stirred overnight at RT and purified by column

chromatography to give 12 mg (29%) of prodrug **I-S22-PD2** as an off white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.25 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.22 (s, 3H), 2.36 - 2.41 (m, 1H), 2.49 (s, 3H), 2.57 - 2.63 (m, 5H), 2.86 - 2.89 (m, 2H), 2.93 (t, 2H, J = 6.5 Hz), 3.79 (d, 1H, J = 7.0 Hz), 4.20 - 4.44 (m, 7H), 4.98 (d, 1H, J = 8.0 Hz), 5.53 (d, 1H, 3.0 Hz), 5.69 (d, 1H, J = 7.0 Hz), 6.02 (dd, 1H, J = 9.5 Hz, J = 3.0 Hz), 6.26-6.29 (m, 2H), 7.20 (d, 1H, J = 9.0 Hz), 7.33 - 7.62 (m, HH), 7.74 (d, 2H, J = 7.5 Hz), 8.14 (d, 2H, J = 7.5 Hz). MS (ES⁺) m/z: 1134.44 [M+H]⁺; 1156.56 [M+Na]⁺.

Water solubility: Paclitaxel and its prodrug **I-S22-PD2** (2 mg each) were suspended in 1 mL water or PBS-buffer (pH 7.4). The suspensions were sonicated for 15 min and centrifuged (13,000 g) for 10 min. The supernatant was analyzed using HPLC.

HPLC: Waters RP18 column (150 x 3.9 mM, X-Terra); DAD-HP Agilent (Model 1100); eluent: CH₃CN/H₂O (gradient 0-100% acetonitrile in 0-15 min). The uv-detector was set at 210 nm. The concentrations were determined by measuring the relative area of paclitaxel or **I-S22-PD2**. It was observed that the solubility of **I-S22-PD2** was 20 times more than that of paclitaxel. (i.e, ~0.2 mg/mL).

The following double/mutual prodrugs (Examples 44 - 80) were synthesized by the methods depicted in Schemes 17-21, using appropriate therapeutic agents and obvious modifications:

Example 44

Synthesis of mutual prodrug of desloratidine and pseudoephedrine (I-AA-MPD1):

This mutual prodrug was synthesized as depicted in Scheme 21. The compound **I-AA-MPD1** was obtained as a colorless gum. ¹H-NMR (300 MHz, CDCl₃): δ 1.00 (d, 3H, J = 6.9 Hz), 2.27-2.51 (m, 4H), 2.74-2.97 (m, 9H), 3.28-3.41(m, 4H), 3.79 (bs, 2H), 4.28-4.30 (m, 4H), 4.57 (m, 1H), 7.04-7.44 (m, 9H), 8.26-8.33 (m, 2H). MS (m/z): 682 [M+H]⁺.

Example 45

Synthesis of mutual prodrug of amlodipine and lisinopril (I-AA-MPD2):

Step 1: Synthesis of diethyl ester of lisinopril:

To a suspension of lisinopril (10.0 g, 22.62 mmol) in ethanol (150 mL) was added SOCl₂ (4.95 mL, 67.94 mmol) and refluxed for 1.5 h. An additional 1 mL of SOCl₂ was added to the mixture every hour for 4 h. The mixture was concentrated and azeotroped with

benzene. The resulting hydrochloride was basified with saturated NaHCO_3 and extracted with EtOAc. Usual aqueous work-up gave 12.86 g of lisinopril diethyl ester, which was used without purification. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.23-1.64 (m, 10H), 1.89-2.3 (m, 6H), 2.63-2.66 (m, 2H), 2.80 (bs, 2H), 3.19 (t, 2H, $J = 7.5$ Hz), 3.36-3.59 (m, 6H), 4.12-4.19 (m, 4H), 4.4-4.5 (m, 1H), 7.14-7.28 (m, 5H). MS [m/z]: 462.4 $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of **I-AA-MPD2**: CDI (1.23 g, 7.64 mmol) was added to a solution of **I-A1-PD2** (Example 18) (3.0 g, 5.09 mmol) in DMF (10 mL) and stirred RT for 3.5 h. A solution of lisinopril diethyl ester (2.34 g, 5.09 mmol) in DMF (5 mL) was added and stirred at 65°C for 8 h. The reaction was quenched with brine and taken up in EtOAc.

After usual aqueous work-up and chromatographic purification, 2.5 g (45%) of **I-AA-MPD2** were obtained. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.17 (t, 3H, $J = 7.5$ Hz), 1.24-1.30 (m, 7H), 1.45-1.80 (m, 7H), 1.90-2.30 (m, 7H), 2.36 (s, 3H), 2.70 (bs, 2H), 2.89-2.95 (m, 4H), 3.10-3.20 (bs, 3H), 3.40-3.70 (m, 9H), 4.00-4.40 (m, 10H), 4.47-4.53 (m, 1H), 4.68-4.73 (q, 2H, $J = 13$ Hz), 5.30 (bs, 1H), 5.39 (s, 1H), 5.65 (bs, 1H), 7.15-7.36 (m, 9H). MS (m/z): 1076 $[\text{M}+\text{H}]^+$, 1098 $[\text{M}+\text{Naf}]$.

Example 46

Synthesis of mutual prodrug of amlodipine and losartan (**I-AA-MPD3a**):

This mutual prodrug was synthesized as described in Example 34, with obvious modifications, using the appropriate amino containing therapeutic agents. The product **I-AA-MPD3a** was obtained as a cream color solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.86 (t, 3H, $J = 6.6$ Hz), 1.16 (t, 3H, $J = 7.1$ Hz), 1.31 (m, 2H), 1.60 (m, 2H), 2.31 (s, 3H), 2.48 (t, 2H, $J = 7.9$ Hz), 2.80-2.92 (m, 4H), 3.40 (m, 4H), 3.56 (s, 3H), 4.01 (m, 2H), 4.32 (m, 4H), 4.68 (q, 2H, $J = 6.5$ Hz), 5.00 (s, 2H), 5.14 (s, 2H), 5.37 (s, 1H), 6.90 (d, 1H, $J = 7.8$ Hz), 7.02-7.22 (m, 5H), 7.33-7.43 (m, 3H), 7.50-7.60 (m, 2H). MS (m/z): 1037 $[\text{M}-\text{H}]^-$.

Example 47

Synthesis of mutual prodrug of celecoxib and valdecoxib (**I-AA-MPD4**):

This mutual prodrug was synthesized by reacting the imidazolidine intermediate of **I-A3-PDI** with valdecoxib according to method described in Scheme 17 with appropriate modifications. This mutual prodrug **I-AA-MPD4** was obtained as a white solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.16 (s, 3H), 2.29 (s, 3H), 2.71 (bs, 4H), 4.14 (bs, 4H), 6.69 (s, 2H), 7.02-7.33 (m, 14H), 7.97 (d, 3H, $J = 9.0$ Hz). MS (m/z): 900 $[\text{M}-\text{H}]^-$.

Example 48**Synthesis of double prodrug of valdecoxib (I-AA-MPD5):**

This double prodrug was synthesized by reacting I-A3-PD1 and valdecoxib using the method B described in Scheme 13. The double prodrug I-AA-MPD5 was obtained as an off white solid. ¹H-NMR (300 MHz, CDCl₃): δ 2.40 (s, 6H), 2.82 (bs, 4H), 4.20 (bs, 4H), 7.20-7.35 (m, 14H), 7.97 (d, 4H, J = 9.0 Hz). MS (m/z): 833[M-H]⁻.

Example 49**Synthesis of double prodrug of valdecoxib (I-AA-MPD8a):**

This mutual prodrug was synthesized using succinic anhydride and valdecoxib according to method B described in Scheme 13 with appropriate modifications. This double prodrug I-AA-MPD8a was obtained as an off-white solid. ¹H-NMR (300 MHz, CDCl₃): δ 2.46 (s, 6H), 2.58 (s, 4H), 7.25-7.37 (m, 16H), 7.95 (d, 2H, J = 9.0 Hz). MS (m/z): 709 [M-H]⁻.

Example 50

Synthesis of double prodrug of valdecoxib (I-AA-MPD8b):

This mutual prodrug was synthesized using glutaric anhydride and valdecoxib according to method B described in Scheme 13 with appropriate modifications. This double prodrug I-AA-MPD8b was obtained as a colorless gum. ¹H-NMR (300MHz, CDCl₃ + CD₃OD): δ 1.68-1.74 (m, 2H), 2.15 (t, 4H, J = 4.5 Hz), 2.38 (s, 6H), 7.01 (bs, 1H), 7.17-7.30 (m, 14H), 7.50 (bs, 1H), 7.88 (d, 4H, J = 8.58 Hz). MS (m/z): 723 [M-H]⁻.

Example 51**Synthesis of mutual prodrug of olanzapine and fluoxetine (I-AA-MPD9):**

This mutual prodrug was made according to Scheme 17 with appropriate modifications. This mutual prodrug I-AA-MPD9 was obtained as a yellow gum. ¹H-NMR (300 MHz, CDCl₃): δ 2.05-2.20 (m, 2H), 2.40 (s, 3H), 2.44 (s, 3H), 2.50-2.90 (m, 12H), 3.30-3.80 (m, 4H), 4.10-4.50 (m, 4H), 5.20 (bs, 1H), 6.42 (s, 1H), 6.87 (d, 2H, J = 8.52 Hz), 7.04-7.36 (m, 9H), 7.42 (d, 2H, J = 8.67 Hz). MS (m/z): 828 [M+H]⁺.

Example 52**Synthesis of double prodrug of gabapentin (I-AA-MPDIOa):**

This double prodrug was synthesized as described below:

Step 1: A solution of SL-I (3.0 g, 19.4 mmol) in DMF (5 mL) was added to a suspension of CDI (9.46 g, 5.83 mmol) in DMF (15 mL) and stirred at RT for 20 h. The mixture was concentrated and the residue purified by column chromatography. The bis-imidazolidine obtained was used as such in the next step.

- 5 Step 2: A solution of the bis-imidazolidine (1.0 g, 2.91 mmol) in acetonitrile (3 mL) was added to a dispersion of gabapentin (1.49 g, 8.75 mmol) in 1N NaHCO₃ (8 mL) and stirred at RT for 3 d. The mixture was diluted with water, acidified with 2N HCl and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 1.04 g (65%) of pure **I-AA-MPD10** was obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.20-1.47 (m, 20H), 2.33 (s, 4H), 2.96 (t, 4H, J = 5.48 Hz), 3.23 (d, 4H, J = 6.5 Hz), 4.31 (t, 4H, J = 6.0 Hz), 5.55 (t, 2H, J = 6.6 Hz). ESI - MS (m/z) : 547 [M-H]⁻.
- 10

Example 53

Synthesis of double prodrug of gabapentin ethyl ester (**I-AA-MPD10b**):

- A mixture of **I-A1-PD8** (2.0 g, 5.26 mmol) and Hunig's base (2.75 mL, 15.8 mmol) in DCM (8 mL) was added to a solution of diphosgene (1.27 mL, 10.53 mmol) in DCM (4 mL) at 0 °C and stirred for 30 min. The mixture was concentrated, dissolved in DCM (10 mL) and treated with a solution of gabapentin ethyl ester hydrochloride (1.86 g, 7.88 mmol) and Hunig's base (2.74 mL, 15.77 mmol) in DCM (10 mL). The mixture was stirred for 3 h. After usual aqueous work-up, the crude material was purified by preparative HPLC to afford 2.2 g (69 %) of **I-AA-MPD10b** as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 6H, J = 6.0 Hz), 1.35-1.67 (m, 20H), 2.33 (s, 4H), 2.91 (t, 4H, J = 6.0 Hz), 3.18 (d, 4H, J = 6.0 Hz), 4.12 (q, 4H, J = 6.0 Hz), 4.29 (t, 4H, J = 6.0 Hz), 5.42 (bs, 2H). MS : ES+ m/z 605 [M+H]⁺, 627 [M+Na]⁺.
- 15
- 20

Example 54

- 25 Synthesis of mutual prodrug of lamotrigine and gabapentin (**I-AA-MPD11**):
- To a solution of **I-A1-PD4** (4.5 g, 10.32 mmol) in acetonitrile (40 mL) at RT was added CDI (2.0 g, 12.38 mmol) and stirred for 3 h. To this was added a solution of gabapentin (2.12 g, 12.38 mmol) in 10 mL of 1% NaHCO₃ solution and the mixture was stirred at RT for 24 h. After usual aqueous work-up and chromatographic purification, 2.6 g (40 %) of **I-AA-MPD11** was obtained as an off white solid. ¹H NMR (CD₃OD, 300 MHz): δ 1.14-1.48 (m, 10H), 2.28 (s, 2H), 2.99 (t, 2H, J = 6.0 Hz), 3.06 (t, 2H, J = 6.3 Hz), 3.22 (s, 2H),
- 30

4.31 (t, 2H, J = 6.0 Hz), 4.46 (t, 2H, J = 6.3 Hz), 7.39-7.49 (m, 2H), 7.69-7.71 (m, 1H).
MS: (ES⁺) m/z 633.1 (M+H)⁺, 655.1 (M+Na)⁺.

Example 55

Synthesis of mutual prodrug of gabapentin ethyl ester and lamotrigine (**I-AA-MPD12**):

- 5 To a suspension of lamotrigine (2.70 g, 10.55 mmol) and DMAP (1.28 g, 10.55 mmol) in toluene (40 mL) at 110 °C was added a solution of the imidazolidine of **I-A1-PD4** (4.99 g, 10.55 mmol) THF (20 mL) and stirred overnight at 110 °C. The reaction mixture was purified by column chromatography to afford 0.85 g (12 %) of **I-AA-MPD12** as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.24 (t, 2H, J = 7.2 Hz), 1.36- 1.77 (m, 10H), 2.29 (s, 2H), 2.93-3.03 (m, 4H), 3.22 (d, 2H, J = 6.6 Hz), 4.11 (q, 2H, J = 7.2 Hz), 4.34 (t, 2H, J = 6.6 Hz), 4.47 (t, 2H, J = 6.3 Hz), 5.65 (t, 1H), 7.34-7.41 (m, 2H), 7.60-7.63 (m, 1H).
10 MS: ES⁺ m/z 661 (M+H)⁺, 682 (M+Na)⁺.

Example 56

Synthesis of mutual prodrug of gabapentin ethyl ester and levetiracetam (**I-AA-MPD13**):

- 15 To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (25 mL) and DCM (5 mL) at RT was added oxalyl chloride (895 mg, 7.05 mmol). The reaction mixture was refluxed for 8 h, after which it was cooled to RT and a solution of **I-A1-PD8** (2.67 g, 7.05 mmol) in DCE (20 mL) was added drop-wise. The resulting mixture was stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 1.63 g (48%) of **I-AA-MPD13** was obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (t, 3H, J = 7.4 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.34-1.52 (m, 10H), 1.82-2.01 (m, 4H), 2.28 (s, 2H), 2.40 (t, 2H, J = 7.0 Hz), 2.89-2.94 (m, 4H), 3.04-3.11 (m, 1H), 3.19 (d, 2H, J = 6.6 Hz), 3.66-3.75 (m, 1H), 4.07-4.16 (m, 3H), 4.27-4.35 (m, 4H), 5.48 (t, 1H, J = 6.5 Hz), 8.18 (bs, 1H). MS: (ES⁺): m/z 576.1 [M+H]⁺; 598.1 [M+Naf. (ES⁻): m/z 574.2 [M-H]⁺.

25 Example 57

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (**I-AA-MPD14**):

This mutual prodrug was synthesized according method outlined in Scheme 18. This mutual prodrug **I-AA-MPD14** was obtained as oil. MS (m/z): 592 [M+H]⁺.

Example 58

- 30 Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (**I-AA-MPD15**):

This mutual prodrug was synthesized according method outlined in Scheme 18. The mutual prodrug **I-AA-MPD15** was obtained as a yellow oil. MS (m/z): 620 [M+H]⁺.

Example 59

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (**I-AA-MPD16**):

- 5 To a suspension of valpromide (750 mg, 5.24 mmol) in DCE (15 mL) at 0-5 °C was added oxalyl chloride (0.5 mL, 6.29 mmol) and refluxed overnight. The reaction mixture was cooled to RT, treated with a solution of **I-A1-PD8** (2.18 g, 5.76 mmol) in DCE (2 mL) and stirred at RT for 2 h. The reaction mixture was purified by column chromatography to afford 1.61 g (51%) of **I-AA-MPD16** as a colorless oil. ¹H NMR
- 10 (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.09 Hz), 1.25 (t, 3H, J = 6.96 Hz), 1.31-1.69 (m, 18H), 2.29 (s, 3H), 2.89-2.99 (m, 4H), 3.20 (d, 2H, J = 6.47 Hz), 4.13 (q, 2H), 4.33 (t, 2H, J = 6.71 Hz), 4.40 (t, 2H, J = 5.97 Hz), 5.54 (t, 1H), 8.29 (br s, 1H). MS: ES+ m/z 549 [M+H]⁺, 571 [M+Na]⁺.

Example 60

- 15 Synthesis of double prodrug of valproic acid (**I-AA-MPD22**):

To a suspension of valpromide (3.0 g, 20.95 mmol) in DCE (30 mL) at 0-5 °C was added oxalyl chloride (1.3 mL, 15.08 mmol) and refluxed overnight. The reaction mixture was cooled to RT, a solution of **SL-I** (0.808 g, 5.24 mmol) in DCE (3 mL) was added and stirred overnight. After usual work-up and chromatographic purification, 1.97 g (43%) of

20 **I-AA-MPD22** were obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 12H, J = 7.18 Hz), 1.28-1.66 (m, 16H), 2.94-2.95 (m, 2H), 3.02 (t, 6H, J = 6.51 Hz), 4.42 (t, 4H, J = 6.47 Hz). MS: m/z 493.2 [M+H]⁺, 510.0 [M+NH₄]⁺, 515.10 [M+Naf].

Example 61

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (**I-AA-MPD27**):

- 25 Step 1: To a solution of **I-A1-PD8** (4.0 g, 10.54 mmol) in THF (25 mL) was added CDI (2.22g, 13.7 mmol) and stirred at RT for 90 min. To this was added t-butyl carbazate (1.39 g, 10.54 mmol) and DMAP (1.288 g, 10.54 mmol), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.0 g (91%) of the intermediate boc-hydrazide was obtained as a colorless gummy material. ¹H NMR
- 30 (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.31-1.74 (m, 10H), 2.30 (s,

2H), 2.90-3.01 (m, 4H), 3.20 (d, 2H, J = 6.6 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.32 (t, 2H, J = 6.5 Hz), 4.39 (t, 2H, J = 6.5 Hz), 5.42 (br s, 1H), 6.04 (br s, 1H), 6.98 (br s, 1H).

Step 2: To a solution of the above boc-hydrazide (4.0 g, 7.44 mmol) in DCM (20 mL) was added 50% TFA/DCM (10 mL) and stirred at RT for 1h. DCM was removed under vacuum, the resulting residue triturated with diethyl ether (2 x 20 mL) and dried to give a colorless oil, which was dissolved in THF (20 mL). To the above solution at 0-5 °C was added TEA (2.1 mL, 14.88 mmol), valproic acid (1.18 g, 8.184 mmol), DCC (2.3 g, 11.16 mmol) and DMAP (0.909 g, 7.44 mmol) and the mixture was stirred overnight at RT. The mixture was filtered, concentrated and purified by column chromatography to afford 2.59 g (51 %) of **I-AA-MPD27** as a colorless gummy material. ¹H NMR (CDCl₃, 300 MHz): δ 0.85 (t, 6H, J = 7.2 Hz), 1.3 (t, 6H, J = 7.11 Hz), 1.21-1.80 (m, 26H), 2.2-2.3 (m, 1H), 2.35 (s, 2H), 2.81-2.94 (m, 4H), 3.21 (d, 2H, J = 6.6 Hz), 3.65-3.68 (m, 1H), 4.19 (q, 2H, J = 7.11 Hz), 4.36 (t, 2H, J = 6.51 Hz), 4.39 (t, 2H, J = 6.51 Hz), 5.51 (t, 1H), 8.17 (s, 1H). MS: m/z 712 [M+Naf], 728 [M+K]⁺, 688 [M-H]⁻.

15 Example 62

Synthesis of mutual prodrug of valproic acid and nicotinic acid (I-CC-MPD1):

Step 1: To a solution of nicotinyl chloride hydrochloride (3.16 g, 17.76 mmol) and **LI-2c** (3 g, 11.84 mmol) in THF (50 mL) was added TEA (8.3 mL, 59.2 mmol) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.14 g (97%) of **LI-2c-nicotinate** ester was obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.43 (s, 9H), 2.82 (t, 2H, J = 6.31 Hz), 3.42-3.48 (q, 2H), 4.62 (t, 2H, J = 6.59 Hz), 7.29-7.33 (m, 1H), 8.30 (d, 1H, J = 7.95 Hz), 8.78 (dd, 1H, J = 4.86, 1.72 Hz), 9.23 (d, 1H, J = 2.13 Hz). MS: m/z 358 [M+H]⁺, 381 [M+Naf], 739 [2M+Na]⁺.

Step 2: To a solution of **LI-2c-nicotinate** ester (0.92 g, 2.50 mmol) in DCM (5 mL) was added 50% TFA/DCM (5 mL) and stirred for 1h. Reaction mixture was concentrated and the residual TFA salt was used as such in Step 3.

Step 3: To a solution of valproic acid (0.37 g, 2.56 mmol) in THF (5 mL) was added CDI (0.5 g, 3.08 mmol) and stirred for 2h. This was treated with a solution of the above TFA salt, TEA (0.7 mL, 5.13 mmol) and DMAP (50 mg, 0.41 mmol) in THF (10 mL) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.7 g (71%) of **I-CC-MPD1** was obtained as a white solid. ¹H NMR

(CDCl₃, 500 MHz): δ 0.88 (t, 6H, J = 7 Hz), 1.25-1.59 (m, 8H), 2.06-2.08 (ro, 1H), 2.86 (t, 2H, J = 6 Hz), 3.05 (t, 2H, J = 7 Hz), 3.58-3.61 (q, 2H, J = 9.0 Hz), 4.63 (t, 2H, J = 6.5 Hz), 7.40-7.42 (m, 1H), 8.30 (dt, 1H, J = 8.0, 2.0 Hz), 8.79 (dd, 1H, J = 5.0, 2.0 Hz), 9.23 (d, 1H, J = 0.5 Hz). MS: m/z 385 [M+H]⁺, 407 [M+Naf], 423 [M+K]⁺.

5 Example 63

Synthesis of mutual prodrug of valproic acid and nicotinic acid (**I-CC-MPD2**):

This mutual prodrug was synthesized as described in Example 62, with obvious modifications. 0.612 g (41%) of **I-CC-MPD2** was obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.23 Hz), 1.24-1.62 (m, 8H), 2.34-2.42 (m, 1H), 2.92 (t, 2H, J = 6.83 Hz), 2.98 (t, 2H, J = 6.04 Hz), 3.78-3.84 (q, 2H), 4.37 (t, 2H, J = 6.79 Hz), 7.36-7.41 (m, 1H), 8.15 (d, 1H, J = 7.92 Hz), 8.73 (d, 1H, J = 4.78 Hz), 9.02 (s, 1H). MS: m/z 385 [M+H]⁺, 419 [MH-HCl]⁺, 383 [M-H]⁻.

Example 64

Synthesis of mutual prodrug of zidovudine and lamivudine (**I-HH-MPD1**):

15 Step 1: Synthesis of intermediate **I-S17-PDI1**:

4-Nitrophenyl chloroformate (0.27 g, 1.34 mmol) was added to a solution of the **I-HI-PD5** (0.4 g, 0.89 mmol) and pyridine (76 μ L, 1 mmol) in DCM (10 mL) and stirred at RT for 15 h. The mixture was concentrated and the residue purified by column chromatography to give 0.29 g (53%) of **I-S17-PDI1**. ¹H-NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H), 2.45 (m, 2H), 2.97-3.06 (m, 4H), 4.05 (m, 1H), 4.41 (m, 1H), 4.40-4.49 (m, 4H), 4.54 (t, 2H, J = 6.5 Hz), 6.17 (t, 1H, J = 6.0 Hz), 7.33 (s, 1H), 7.39 (d, 2H, J = 4.8 Hz), 8.28 (d, 2H, J = 4.8 Hz) and 8.50 (s, 1H). MS (m/z): 635 [M+Naf].

Step 2: Synthesis of **I-HH-MPD1**: Lamivudine (45 mg, 0.196 mmol) and DMAP (48 mg, 0.39 mmol) were added to a solution of **I-S17-PDI1** (80 mg, 0.13 mmol) in DMF (1.5 mL) and stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography to give 40 mg (43%) of product **I-HH-MPD1**. ¹H-NMR (300 MHz, CDCl₃): δ 1.90 (s, 3H), 2.45 (t, 2H, J = 6.1 Hz), 3.05 (t, 4H, J = 6.2 Hz), 3.20 (m, 1H), 3.53 (m, 1H), 4.08 (m, 1H), 4.30-4.80 (m, 8H), 5.45 (t, 1H, J = 3.0 Hz), 5.90 (d, 1H, J = 7.5 Hz), 6.17 (t, 1H), 6.30 (t, 1H), 7.55 (s, 1H) and 7.90 (d, 1H, J = 7.50 Hz). MS (m/z): 725 [M+Naf].

Example 65

Synthesis of mutual prodrug of zidovudine and lamivudine (**I-HH-MPD2b**):

This mutual prodrug was synthesized according to the method outlined in Scheme 18.

The mutual prodrug **I-HH-MPD2b** was obtained as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 1.97 (s, 3H), 2.42 (m, 2H), 2.90-2.94 (m, 16H), 3.06 (m, 1H), 3.40-3.44 (m, 8H), 3.50-3.56 (m, 1H), 3.71-3.73 (m, 1H), 4.95 (m, 1H), 4.27-4.30 (m, 4H), 4.37-4.49 (m, 4H), 5.32 (t, 1H, J = 5.1 Hz), 5.83 (d, 1H, J = 6.6 Hz), 6.07 (m, 1H), 6.33 (bs, 1H), 7.20-7.25 (m, 1H), 7.74 (m, 1H). MS (m/z): 954 [MH-Na]⁺.

Example 66

10 Synthesis of mutual prodrug of cetirizine and pseudoephedrine (**I-CA-MPD1**):

Step 1: Synthesis of intermediate **I-S17-PDI1**:

This intermediate was prepared by reacting **I-C1-PD10** with p-nitrophenyl chloroformate by a procedure similar to that described in Example 64. The desired intermediate **I-S17-PDI1** was obtained as a gum. ¹H-NMR (300 MHz, CDCl₃): δ 2.49-2.71 (m, 10H), 2.95 (t, 2H, J = 6.6 Hz), 3.01 (t, 2H, J = 6.5 Hz), 3.73 (bs, 2H), 4.13 (s, 2H), 4.22 (s, 1H), 4.41 (t, 2H, J = 6.6 Hz), 4.53 (t, 2H, J = 6.6 Hz), 7.18-7.40 (m, 11H), 8.28 (d, 2H, J = 7.1 Hz).

Step 2: The mutual prodrug **I-CA-MPD1** was synthesized by reacting intermediate **I-S17-PDI1** with pseudoephedrine by a procedure similar to that described in Example 64, Step 2. The desired mutual prodrug **I-CA-MPD1** was obtained as a colorless gummy material. ¹H-NMR (300 MHz, CDCl₃): δ 0.99-1.09 (d, 3H, J = 6.6 Hz), 2.45 (bs, 4H), 2.68 (bs, 6H), 2.90 (s, 3H), 2.91-2.94 (m, 4H), 3.71 (bs, 3H), 4.11 (s, 2H), 4.18 (s, 1H), 4.26-4.41 (m, 4H), 4.56 (m, 2H), 7.17-7.35 (m, 12H). MS (m/z): 716 [M+H]⁺.

Example 67

Synthesis of mutual prodrug of gabapentin ethyl ester and naproxen (**I-CA-MPD5**):

25 This mutual prodrug was synthesized by reacting **I-A1-PD8** and Naproxen using Scheme 11, Method B. This mutual prodrug was obtained as colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, J = 7.1 Hz), 1.30-1.55 (m, 10H), 1.57 (d, 3H, J = 7.1 Hz), 2.27 (s, 2H), 2.84 (q, 4H, J = 6.4 Hz), 3.18 (d, 2H, J = 6.7 Hz), 3.80-3.88 (m, 1H), 3.91 (s, 3H), 4.12 (q, 2H, J = 7.1 Hz), 4.20-4.40 (m, 4H), 5.35 (bt, 1H), 7.05-7.20 (m, 2H), 7.39 (dd, 30 1H, J = 1.8 Hz, 8.4 Hz), 7.60-7.73 (m, 3H). MS (m/z): 592 [M+H]⁺, 614 [M+Na]⁺.

Example 68

Synthesis of mutual prodrug of valproic acid and nicotinic acid (**I-CA-MPD14**):

This mutual prodrug was synthesized using valpromide and nicotinyl chloride hydrochloride, according to the methods described in Scheme 13 and Scheme 17, with obvious modifications. 1.0 g of the mutual prodrug **I-CA-MPD14** was obtained as a yellow oil. ^1H NMR (CD_3OD , 300 MHz): δ 0.87 (t, 6H, $J = 6$ Hz), 1.26-1.75 (m, 9H), 2.83 (s, 1H), 2.95-3.0 (m, 4H), 3.81 (t, 2H, $J = 6$ Hz), 4.44 (t, 2H, $J = 6$ Hz), 7.0 (s, 1H), 7.4 (bs, 1H), 7.42 (m, 1H), 8.20 (d, 1H), 8.65-8.74 (bs, 2H), 9.0 (s, 1H). MS: ES^+ m/z 428.1 $[\text{M}+\text{H}]^+$, 450.1 $[\text{M}+\text{Na}]^+$.

10 Example 69

Synthesis of mutual prodrug of valproic acid and nicotinic acid (**I-CA-MPD15**):

To a solution of **I-C1-PD13** (1.5 g, 4.63 mmol) and nicotinyl chloride hydrochloride (0.99 g, 5.56 mmol) in THF (25 mL) was added TEA (2 mL, 13.89 mmol) at 0 $^\circ\text{C}$ and stirred for 20 h at RT. After usual aqueous work-up and chromatographic purification, 1.0 g (83%) of **I-CA-MPD15** was obtained as a yellow viscous liquid. ^1H NMR (CD_3OD , 500 MHz): δ 0.89 (t, 6H, $J = 5.0$ Hz), 1.29-1.33 (m, 8H), 1.64 (bs, 2H), 3 (t, 2H, $J = 5.0$ Hz), 3.07 (t, 2H, $J = 5.0$ Hz), 4.42 (t, 2H, $J = 5.0$ Hz), 4.63 (t, 2H, $J = 5.0$ Hz), 7.41-7.43 (m, 1H), 8.31 (bs, 1H), 8.78 (bs, 1H), 9.26 (s, 1H). MS: ES^+ m/z 429 $[\text{M}+\text{H}]^+$, 451 $[\text{M}+\text{Na}]^+$, 467 $[\text{M}+\text{K}]^+$.

20 Example 70

Synthesis of mutual prodrug of gabapentin ethyl ester and nicotinic acid (**I-CA-MPD18**):

To a solution of **I-S12-PD2** (synthesized as described in Scheme 12, Method C) (3.76 g, 7.64 mmol) in THF (30 mL) was added nicotinyl chloride hydrochloride (1.5 g, 8.40 mmol), followed by TEA (4.26 mL, 30.56 mmol) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.87 g (23 %) of **I-CA-MPD18** was obtained as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.24 (t, 3H, $J = 6.0$ Hz), 1.27-1.47 (m, 10H), 2.27 (s, 2H), 2.90-3.17 (m, 4H), 3.16 (d, 2H, $J = 6.0$ Hz), 3.79 (q, 2H, $J = 6.0$ Hz), 4.10 (q, 2H, $J = 6.0$ Hz), 4.36 (t, 2H, $J = 6.0$ Hz), 5.56 (bt, 1H, $J = 6.0$ Hz), 7.32-7.38 (m, 1H), 8.17(d, 1H, $J = 9.0$ Hz), 8.71 (d, 1H, $J = 6.0$ Hz), 9.07 (s, 1H). MS: $(\text{ES})^+$ m/z 484 $(\text{M}+\text{H})^+$, 506 $(\text{M}+\text{Na})^+$; $(\text{ES})^-$ m/z 482 $(\text{M}-\text{H})^+$.

Example 71

Synthesis of mutual prodrug of levetiracetam and valproic acid (**I-CA-MPD19**):

To a solution of levetiracetam (**1.0 g**, 5.87 mmol) in DCE (20mL) and DCM (4mL) was added oxalyl chloride (894 mg, 7.05 mmol) and heated at 80 °C for 7h. The reaction mixture was cooled to RT, a solution of **I-C1-PD11** (1.97 g, 7.05 mmol) in DCE (10mL) was added and stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 1.73 g (61 %) of **I-CA-MPD19** was obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.85-0.91 (m, 9H), 1.24-1.62 (m, 8H), 1.80-2.05 (m, 4H), 2.34-2.44 (m, 3H), 2.91 (t, 4H, J = 6.0 Hz), 3.03-3.12 (m, 1H), 4.06-4.09 (m, 1H), 4.31-4.36 (m, 4H), 8.32 (bs, 1H). MS: (ES⁺) m/z 477.1 [M+H]⁺, 498.9 [M+Na]⁺ (ES)⁻ m/z 475.0 [M-H]⁻.

Example 72

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (**I-CA-MPD21**):

This mutual prodrug was synthesized by following a route depicted in Scheme 19, with obvious modifications. The mutual prodrug **I-CA-MPD21** was obtained as a colorless oil. ¹H-NMR (CDCl₃, 300 MHz): δ 0.81 (t, 6H, J = 7.19 Hz), 1.15-1.60 (m, 21H), 2.20 (s, 2H), 2.25-2.35 (m, 1H), 2.84 (t, 4H, J = 6.6 Hz), 3.11 (d, 2H, J = 6.7 Hz), 4.05 (q, 2H, J = 7.16 Hz and 17.3 Hz), 4.15-4.25 (m, 4H), 5.43 (bt, 1H). MS (m/z): 506 [M+H]⁺, 528 [M+Na]⁺.

Example 73

Synthesis of mutual prodrug of gabapentin ethyl ester and nicotinic acid (**I-CA-MPD22**):

To a suspension of nicotinyl chloride hydrochloride (0.35 g, 1.97 mmol) in THF (3 mL) at 0 °C was added TEA (0.82 mL, 5.91 mmol). After 5 min, a solution of **I-A1-PD8** (0.5g, 1.31 mmol) and TEA (0.27 mL, 1.97 mmol) in THF (4 mL) was added and stirred overnight at RT. The mixture was purified by column chromatography to afford 0.573 g (90 %) of **I-CA-MPD22** as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.24 (t, 3H, J = 6.0 Hz), 1.27-1.47 (m, 10H), 2.27 (s, 2H), 2.94 (t, 2H, J = 6.0 Hz), 3.07 (t, 2H, J = 6.0 Hz), 3.19 (d, 2H, J = 6.0 Hz), 4.12 (q, 2H, J = 6.0 Hz), 4.32 (t, 2H, J = 6.0 Hz), 4.62 (t, 2H, J = 6.0 Hz), 5.29 (bs, 1H), 7.36-7.42 (m, 1H), 8.30 (t, 1H, J = 3.0 Hz), 8.78 (dd, 1H, J = 1.69 Hz), 9.24(s, 1H). MS: (ES)⁺ m/z 485 (M+H)⁺, 507 (M+Na)⁺.

Example 74

Synthesis of mutual prodrug of lamotrigine and valproic acid (**I-CA-MPD23**):

To a suspension of lamotrigine (**0.455 g**, 1.78 mmol) and **DMAP** (0.217 g, 1.78 mmol) in toluene (10 mL) at 110 °C was added a solution of the imidazolide of **I-Cl-PDII** (0.665 g, 1.78 mmol) in THF (5 mL). The reaction was stirred at 110 °C overnight and purified by column chromatography to afford 0.20 g (20%) of **I-CA-MPD23** as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 0.86-0.90 (m, 6H), 1.20-1.44 (m, 6H), 1.53-1.62 (m, 2H), 2.36-2.39 (m, 1H), 2.90-3.0 (m, 4H), 4.34 (t, 2H, J = 6.3 Hz), 4.46 (t, 2H J = 6.6 Hz), 7.36-7.38 (m, 2H), 7.60-7.63 (m, 1H). MS: (ES +) m/z 562 (M+H)⁺, 585 (M +Na)⁺.

Example 75

Synthesis of mutual prodrug of lamotrigine and nicotinic acid (**I-CA-MPD24**):

A solution of **I-A1-PD4** (0.5 g, 1.14 mmol) and TEA (0.5 mL, 2.87 mmol) in THF (5 mL) was added to a suspension of nicotinyl chloride (0.305 g, 1.71 mmol) and 0.5 mL TEA in THF (5 mL). The mixture was stirred at RT for 24 h. After usual aqueous work-up and chromatographic purification, 0.15 g (14%) of **I-CA-MPD24** were obtained as a white solid. ¹H NMR (CDCl₃, 500MHz): δ 3.06 (t, 2H, J = 6.5Hz), 3.10 (t, 2H, J = 6.5 Hz), 4.49 (t, 2H, J = 6.5 Hz), 4.65 (t, 2H, J = 6.5 Hz), 7.38-7.43 (m, 3H), 7.60-7.62 (m, 1H), 8.33-8.36 (m, 1H), 8.81 (m, 1H), 9.35 (bs, 1H). MS: (ES +) m/z 540.9 (M+H)⁺.

Example 76

Synthesis of mutual prodrug of lamotrigine and nicotinic acid (**I-CA-MPD25**):

This mutual prodrug was synthesized using lamotrigine and nicotinyl chloride hydrochloride, according to the methods outlined in Scheme 12 and Scheme 17. 0.8 g (44%) of **I-CA-MPD25.HCl** were obtained as an off white solid. ¹H NMR (D₂O, 500MHz): δ 2.93 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.0Hz), 3.69 (t, 2H, J = 6.5Hz), 4.49 (m, 2H), 7.37-7.43 (m, 3H), 7.69-7.71 (m, 1H), 8.05-8.07 (m, 1H), 8.78-8.79 (m, 1H), 9.30 (bs, 1H). MS: (ES +) m/z 539.9 (MH-H)⁺, 561.8 (M +Na)⁺.

Example 77

Synthesis of mutual prodrug of metronidazole and norfloxacin (**I-AH-MPD1**):

Step 1: Synthesis of imidazolide of **I-H1-PD1**:

CDI (319 mg, 1.97 mmol) was added to a solution of **I-H1-PD1** (577 mg, 1.64 mmol) in DMF (8 mL) and stirred at RT for 4 h. The mixture was concentrated and the residue

purified by column chromatography to give 395 mg (54%) of the imidazolidine of I-HI-**PD1**. ¹H-NMR (300 MHz, CDCl₃): δ 2.50 (s, 3H), 2.92 (t, 2H, J = 6.0 Hz), 3.00-3.10 (m, 2H), 4.36 (t, 2H, J = 3.0 Hz), 4.47-4.51 (m, 2H), 4.57-4.70 (m, 4H), 7.07 (s, 1H), 7.43 (s, 1H), 7.95 (s, 1H), 8.15 (s, 1H). MS (m/z): 446 [M+H]⁺.

- 5 Step 2: Synthesis of **I-AH-MPD1**: A solution of the imidazolidine of **I-HI-PD1** (100 mg, 0.224 mmol) in DMF (1 mL) was added to a suspension of norfloxacin (86 mg, 0.269 mmol) in DMF (2 mL) and stirred at RT for 60 h. The mixture was concentrated and the residue purified by column chromatography to give 35 mg (22%) of **I-AH-MPD1**. ¹H-NMR (300 MHz, CDCl₃): δ 1.59 (t, 3H, J = 7.5 Hz), 2.53 (s, 3H), 2.86-2.97 (m, 4H),
10 3.27-3.30 (m, 4H), 3.72 (t, 4H, J = 4.5 Hz), 4.32-4.40 (m, 6H), 4.48-4.52 (m, 2H), 4.59-4.63 (m, 2H), 6.85 (d, 1H, J = 6.0 Hz), 7.96 (s, 1H), 8.09 (d, 1H, J = 12.0 Hz), 8.68 (s, 1H). MS (m/z): 697 [M+H]⁺.

The following mutual prodrugs (Examples 78 - 80) were obtained according to procedures similar to those described in Example 77, with the substitution of the
15 appropriate pairs of amino-containing and hydroxyl-containing therapeutic agents:

Example 78

Synthesis of mutual prodrug of metronidazole and norfloxacin (**I-AH-MPD3b**):

- The mutual prodrug **I-AH-MPD3b** was obtained as a yellow solid. ¹H-NMR (300MHz, CDCl₃): δ 1.59 (t, 3H, J = 7.1 Hz), 2.49 (s, 3H), 2.82-2.98 (m, 10H), 3.30 (t, 4H, J = 4.5 Hz), 3.39 (bs, 4H), 3.72 (t, 4H, J = 4.8 Hz), 4.38 (dt, 8H, J = 26.2, 6.4 Hz), 4.61 (t, 2H, J = 4.8 Hz), 6.86 (d, 1H, J = 6.4 Hz), 7.95 (s, 1H), 8.07 (bd, 1H, J = 12.8 Hz), 8.67 (s, 1H), 14.9 (s, 1H). MS (m/z): 811.26 [M+H]⁺.
- 20

Example 79

Synthesis of mutual prodrug of gabapentin and tramadol (**I-AH-MPD7**):

- 25 The mutual prodrug was synthesized according to the method in Scheme 15 with obvious modifications. The mutual prodrug **I-AH-MPD7** was obtained as a colorless gummy material. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, J = 7.1 Hz), 1.32-2.45 (m, 30H), 2.91-2.99 (m, 4H), 3.16 (t, 2H, J = 7.3 Hz), 3.80 (s, 3H), 4.08-4.15 (q, 2H, J = 7.1 Hz), 4.28-4.40 (m, 4H), 5.4 (t, 1H), 6.74-6.81 (m, 3H), 7.23-7.29 (t, 1H, J = 8 Hz). MS (m/z):
30 669.30 [M+H]⁺.

Example 80

Synthesis of mutual prodrug of venlafaxine and paroxetine (**I-AH-MPD8**)

The mutual prodrug was synthesized according to the method outlined in Scheme 15 with obvious modifications. The mutual prodrug **I-AH-MPD8** was obtained as a white sticky solid. ¹H-NMR was consistent with the expected structure. MS: m/z 812 [M]⁺.

5 Example 81

Synthesis of NO-releasing prodrug of Valproic acid (**I-C1-NOPD1**):

This prodrug was synthesized as shown in Scheme 11, Method B using as reagents valproic acid (725 mg, 5.03 mmol), **LI-2b** (1 g, 5.03 mmol), TEA (611 mg, 6.04 mmol), DCC (1.25 g, 6.04 mmol) and DMAP (100 mg). Yield: 832 mg (51%). ¹H-NMR (300
10 MHz, CDCl₃): δ 0.89 (t, 6H, J = 7.09 Hz), 1.22-1.77 (m, 8H), 2.36-2.40 (m, 1H), 2.93-3.00 (m, 4H), 4.34 (t, 2H, J = 6.8 Hz), 4.70 (t, 2H, J = 6.35 Hz). MS (CI)⁺ m/z: 326 [M+H]⁺.

Example 82

Synthesis of NO-releasing prodrug of valproic acid (**I-C1-NOPD3a**):

15 This prodrug was prepared as shown in Scheme 13, Method A. Thus, to a stirred mixture of valproyl isocyanate, which was freshly prepared from valpromide (0.7 g, 4.90 mmol [valpromide was synthesized from valproic acid by using known methods as shown in Scheme 11, Method I) using a known method (see *J. Org. Chem.*, 1962, 27, 3742) in DCM (20 mL) at RT was added a solution of **LI-2b** (0.976 g, 4.90 mmol) in DCM (5
20 mL) drop-wise and stirred at RT for 2 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 0.6 g (33%) of prodrug **I-C1-NOPD3a**. ¹H-NMR data is consistent with the expected structure. MS: [ES]⁺ m/z 391 [M+Na]⁺, 407.2 [M+K]⁺; [EI]⁺ m/z 368 [M + H]⁺.

Example 83

25 Synthesis of NO-releasing prodrug of aspirin (**I-C1-NOPD4**):

This prodrug was synthesized as shown in Scheme 11, Method D. Thus, to a solution of aspirin (3.0 g, 16.65 mmol) in THF (30 mL) at 0 °C was added oxalyl chloride (1.86 mL, 21.64 mmol) and heated at 70 °C for 2 h. The mixture was concentrated, the residue was dissolved in THF (30 mL) and treated with a solution of **LI-2a** (3.61 g, 16.65 mmol),
30 TEA (3.48 mL, 24.97 mmol) and DMAP (361 mg) in THF (20 mL). The resulting mixture was stirred at RT for 2 h and filtered through celite. The filtrate was concentrated

and the residue purified by column chromatography to afford 3.06 g (48%) of the bromide **SII-II**. ¹H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 3.01-3.12 (m, 4H), 3.61 (t, 2H, J = 6.5 Hz), 4.53 (t, 2H, J = 6.0 Hz), 7.11 (dd, 1H, J = 8 Hz, 1 Hz), 7.32 (t, 1H, J = 7.6 Hz), 7.57 (t, 1H, J = 7.6 Hz), 8.03 (dd, 1H, J = 7.8 Hz, 1.6 Hz). MS (ES⁺) m/z: 403.92 (M+Na)⁺.

To a solution of **SII-II** (2.0 g, 5.27 mmol) in acetonitrile (20 mL) at 0 °C was added AgNO₃ (1.07 g, 6.32 mmol) in the dark. The mixture was stirred at RT for 1.5 h, filtered through celite and concentrated. The residue, after usual aqueous work-up and chromatographic purification, afforded 0.965 g (50%) pure **I-C1-NOPD4**. ¹H-NMR (300 MHz, CDCl₃): δ 2.36 (s, 3H), 2.98 (t, 2H, J = 6.8 Hz), 3.05 (t, 2H, J = 6.4 Hz), 4.54 (t, 2H, J = 6.4 Hz), 4.70 (t, 2H, J = 6.8 Hz), 7.12 (d, 1H, J = 8 Hz), 7.33 (t, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.5 Hz), 8.03 (dd, 1H, J = 7.8 Hz, 1 Hz). MS (ES)⁺ m/z: 379.11 (M+NH₄)⁺, 383.98 (M+Na)⁺.

Example 84

15 Synthesis of NO-releasing prodrug of aspirin (I-CI-NOPD5a):

As shown in Scheme 11, Method H, this prodrug was synthesized in three steps:

Step 1: To a suspension of aspirin (1 g, 5.55 mmol) in benzene (15 mL) and DMF (1 drop) at 0-5 °C was added a solution of oxalyl chloride (0.6 mL, 6.66 mmol) in benzene (5 mL) and stirred at 85 °C for 2 h. The reaction mixture was concentrated, and the crude acid chloride was used immediately in the next step.

Step 2: To a solution of the above acid chloride in benzene (30 mL) was added silver cyanate (998 mg, 6.66 mmol) and refluxed in the dark for 1 h. The mixture, containing 2-acetoxybenzoyl isocyanate, was cooled to RT and used in the next step.

Step 3: To the above mixture was added a solution of **LI-2b** (1.33 g, 6.66 mmol) in benzene (5 mL) and stirred at RT for 1h. The mixture was filtered through celite and concentrated, and the residue was purified by column chromatography to afford 1.2 g (54%) of pure **I-CI-NOPD5a**. ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 404.98 [M+H]⁺, 426.94 [M+Na]⁺, 442.97 [M+K]⁺, (ES⁻) m/z: 403.01 [M-H]⁻.

30 Example 85

Synthesis of sodium salt of NO-releasing prodrug of aspirin (I-CI-NOPD5b):

To a suspension of 60% sodium hydride (45 mg, 1.3 mmol) in THF (0.5 mL) was added solution of **I-C1-NOPD5a** (500 mg, 1.24 mmol) in THF (1.5 mL). After stirring for 5 min, THF was removed under vacuum, the residue was washed with dry Et₂O (4 x 3 mL) to remove unreacted starting material and dried in vacuum to afford 410 mg (78%) of **I-C1-NOPDSb** as an off-white solid. ¹H NMR (D₂O, 500 MHz): δ 2.28 (s, 3H), 2.93-2.97 (m, 4H), 4.33 (t, 2H, J = 6.0 Hz), 4.68 (t, 2H, J = 7.2 Hz), 7.07 (d, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 7.5 Hz), 7.41 (t, 1H, J = 9.0 Hz), 7.57 (d, 1H, J = 7.5 Hz). MS: m/z 427.0 [M+H]⁺, 449.0 [M+Na]⁺.

Example 86

10 Synthesis of NO-releasing prodrug of aspirin (**I-C1-NOPD6**):

This prodrug was synthesized as shown in Scheme 11, Method E. Thus, to a solution of aspirin (1.20g, 6.70 mmol) in DCM (15 mL) at 0 °C was added oxalyl chloride (0.74 mL, 8.65 mmol) and stirred at RT for 1.5 h. The mixture was concentrated and the residual acid chloride was treated with **LI-5.TFA** (6.70 mmol) in DCM (14 mL), followed by drop-wise addition of TEA (3.73 mL, 26.81 mmol) at 0 °C. The mixture was stirred at RT for 4 h and concentrated. The residue, after usual aqueous work-up and chromatographic purification, gave 0.822g (34 %) of **I-C1-NOPD6**. ¹H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 2.92 (t, 2H, J = 6.1 Hz), 2.98 (t, 2H, J = 6.0 Hz), 3.76 (q, 2H, J = 6.0 Hz), 4.71 (t, 2H, J = 6.0 Hz), 6.70 (bs, 1H), 7.10 (d, 1H, J = 9.0 Hz), 7.31-7.33 (m, 1H), 7.48-7.50 (m, 1H), 7.78 (d, 1H, J = 6.0 Hz). MS (EI)⁺ m/z: 361 (M+H)⁺.

Example 87

25 Synthesis of NO-releasing prodrug of nicotinic acid (**I-C1-NOPD7**):

This prodrug was synthesized as shown in Scheme 11, Method C. Thus, to a suspension of nicotinyln chloride hydrochloride (2.68 g, 15.07 mmol) in THF (10 mL) at 0 °C was added a solution of **LI-2b** (2.0g, 10.05 mmol) and TEA (5.6 mL, 40.2 mmol) in THF (7 mL) and stirred at RT for 15 h. The mixture was filtered, concentrated and the residue purified by column chromatography to afford 2.23 g (73%) of pure **I-C1-NOPD7**. ¹H-NMR (300 MHz, CDCl₃): δ 3.01 (t, 2H, J = 4.75 Hz), 3.09 (t, 2H, J = 6.5 Hz), 4.63 (t, 2H, J = 5.25 Hz), 4.70 (t, 2H, J = 4.75 Hz), 7.39 - 7.42 (m, 1H), 8.29-8.31 (dt, 1H, J = 8 Hz, 2 Hz), 8.78-8.80 (dd, 1H, J = 2 Hz), 9.23 (d, 1H, J = 2 Hz). MS (ES)⁺ m/z: 305 (M+H)⁺.

Example 88

Synthesis of NO-releasing prodrug of nicotinamide (**I-CI-NOPD8a**):

This prodrug was synthesized from nicotinamide (1 g, 8.18 mmol) according to the procedure described in Example 77 (see Scheme 11, Method I or Scheme 13, Method A).

- 5 After usual workup, the crude product was purified by column chromatography to afford 0.1 g (3.5%) of prodrug **I-CI-NOPD8a**. ¹H-NMR (300 MHz, CDCl₃): δ 2.97-3.0 (m, 4H), 4.51 (t, 2H, J = 6.3 Hz), 4.73 (t, 2H, J = 6.7 Hz), 7.38-7.48 (m, 1H), 8.16-8.22 (m, 1H), 8.71-8.79 (m, 2H), 9.04 (s, 1H). MS [ES]⁺ m/z: 348 [M+H]⁺, 370 [M+Naf].

Example 89

- 10 Synthesis of NO-releasing prodrug of nicotinic acid (**I-C1-NOPD9**):

This prodrug was synthesized as shown in Scheme 11, Method F. Thus, TEA (6.92 mL, 50.55 mmol) was added to a suspension of nicotinyl chloride hydrochloride (3.0 g, 16.85 mmol) and cysteamine hydrochloride (2.1 g, 18.53 mmol) in DCM (30 mL) at 0 °C and stirred at RT for 4 h. The mixture was concentrated and the residue dissolved in MeOH

- 15 (20 mL). To this solution at 0 °C was added a solution of **LI-3b** (4.1 g, 16.85 mmol) in MeOH (5 mL), followed by TEA (4.61 mL, 33.70 mmol) and stirred overnight at RT. The mixture was filtered through celite, concentrated and the residue was purified by column chromatography to afford 3 g (58%) of pure **I-C1-NOPD9**. ¹H-NMR (300 MHz, DMSO-d₆): 2.94 (t, 2H, J = 6.7 Hz), 3.09 (t, 2H, J = 6.3 Hz), 3.56 (q, 2H, J = 6.3 Hz),
20 4.73 (t, 2H, J = 6.3 Hz), 7.49-7.53 (m, 1H), 8.16-8.19 (m, 1H), 8.69-8.70 (m, 1H), 8.87 (br t, 1H), 8.98 (s, 1H). MS (ES⁺) m/z: 304 (M+H)⁺, 326 (M+Na)⁺.

Example 90

Synthesis of NO-releasing prodrug of naproxen (**I-C1-NOPD10**):

This prodrug was synthesized as shown in Scheme 11, Method B. Thus, to a solution of
25 naproxen (2.23 g, 9.7 mmol) and **LI-2b** (1.93 g, 9.7 mmol) in THF (70 mL) at RT were added DCC (3 g, 14.55 mmol) and DMAP (1.78 g, 14.55 mmol) and stirred overnight.

The mixture was filtered and concentrated, and the residue purified by column chromatography to afford 1.03 g (25%) of pure **I-C1-NOPD10**. ¹H-NMR (300 MHz, CDCl₃): δ 1.59 (d, 3H, J = 7.16 Hz), 2.81 (t, 2H, J = 6.77 Hz), 2.87 (t, 2H, J = 6.42 Hz),
30 3.85-3.88 (m, 1H), 3.91 (s, 3H), 4.33 (t, 2H, J = 5.26 Hz), 4.53 (t, 2H, J = 6.79 Hz), 7.10-7.16 (m, 2H), 7.41 (d, 1H, J = 1.7 Hz), 7.69 (t, 3H, J = 8.55 Hz).

Example 91

Synthesis of NO-releasing prodrug of naproxen (**I-C1-NOPD12**):

This prodrug was synthesized as shown in Scheme 11, Method E. Thus, to a solution of
5 naproxen (1.698 g, 7.37 mmol) in chloroform (20 mL) at 0-5 °C was added oxalyl
chloride (0.8 mL, 8.844 mmol), followed by 2-3 drops of DMF. The mixture was stirred
at RT for 90 min and concentrated. This acid chloride (~7.37 mmol) was treated with **LI**-
5.TFA (6.7 mmol) in THF (20 mL) and cooled to 0 °C. To this was added TEA (5.6 mL,
40 mmol) and stirred at RT for 3 h. The mixture was concentrated and the residue, after
10 usual aqueous work-up and chromatographic purification, afforded 0.409 g (14%) of pure
I-C1-NOPD12. ¹H-NMR (CDCl₃, 300 MHz): δ 1.24 (d, 3H), 2.87 (t, 2H, J = 6.5 Hz),
2.93 (t, 2H, J = 6.7 Hz), 3.64 (q, 2H, 7.5 Hz), 3.76 (m, 1H), 3.88 (s, 3H), 4.70 (t, 2H, J =
6.6 Hz), 4.79 (br s, 1H), 6.97-7.08 (m, 3H), 7.35-7.46 (m, 3H).

Example 92

15 Synthesis of NO-releasing prodrug of flurbiprofen (**I-C1-NOPD13**):

This prodrug was synthesized as shown in Scheme 11, Method A, using as reagents
flurbiprofen (4.0 g, 16.37 mmol), CDI (3.97 g, 24.56 mmol) and **LI-2b** (3.25 g, 16.37
mmol). Yield: 3 g (43%). ¹H-NMR (300 MHz, CDCl₃): δ 1.56 (d, 3H, J = 7.2 Hz), 2.80-
3.0 (m, 4H, J = 5.67 Hz), 3.78 (q, 1H, J = 7.10 Hz), 4.36 (m, 2H), 4.66 (t, 2H, J = 6.78),
20 7.11-7.54 (m, 8H).

Example 93

Synthesis of NO-releasing prodrug of flurbiprofen (**I-C1-NOPD14a**):

This prodrug was synthesized as shown in Scheme 11, Method I. Thus, to a solution of
flurbiprofen (5.0 g, 20.46 mmol) in benzene (50 mL), was added oxalyl chloride (3.11 g,
25 24.55 mmol) at 0 °C and 2 drops of DMF and stirred at RT for 20 hrs. Benzene was
removed under vacuum and the residue was diluted with DCM (50mL). The reaction
mixture was cooled to 0 °C and dry ammonia was passed for 30 min. The reaction
mixture was concentrated and, after usual aqueous work-up, 4.5 g of flurbiprofen amide
was obtained as a white solid.

30 To a solution of flurbiprofen amide (3.0 g, 12.33 mmol) in DCM (70 mL) was
added oxalyl chloride (1.87g, 14.79mmol) at 0 °C and refluxed for 16 h. Reaction mixture

was cooled to RT and treated with **LI-2b** (2.45 g, 12.33 mmol) in DCE (10mL) and stirred overnight. After usual aqueous work-up and chromatographic purification, 0.5 g of **I-CI-NOPD14a** were obtained. ¹H NMR (CDCl₃, 300 MHz): δ 1.55 (d, 3H, *J* = 6.9 Hz), 2.94-2.97 (bs, 4H), 4.38-4.47 (bs, 3H), 4.68 (t, 2H, *J* = 6.6 Hz), 7.13-7.55 (bs, 8H)

5 MS: ES⁺ m/z 469.03 [M+H]⁺, 467.16 [M-H]⁺.

Example 94

Synthesis of NO-releasing prodrug of flurbiprofen (I-CI-NOPD15b):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of flurbiprofen (2.5 g, 10.23 mmol) in THF (30 mL) was added CDI (3.31 g, 20.46 mmol) and stirred at RT for 16 h. To this was added **LI-5.TFA** (3.64 g, 10.23 mmol) in THF (15 mL), followed by TEA (2.85 mL, 20.46 mmol) and stirred for 16 h. After usual work-up and chromatographic purification, 1.5 g (91%) of **I-CI-NOPD15b** were obtained. ¹H NMR (CDCl₃, 300 MHz): δ 1.5 (d, 3H, *J* = 6.9 Hz), 2.82 (t, 2H, *J* = 6.3 Hz), 2.92 (t, 2H, *J* = 6.9 Hz), 3.50 (m, 3H), 4.6 (t, 2H, *J* = 6.6 Hz), 5.8 (s, 1H), 7.11-7.55 (bs, 8H). MS: ES⁺ m/z 425.21 [M+H]⁺, 423.11 [M-H]⁺.

Example 95

Synthesis of NO-releasing prodrug of indomethacin (I-CI-NOPD16):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of indomethacin (2.0 g, 5.59 mmol) in chloroform (25 mL) was added CDI (1.09 g, 6.71 mmol) and stirred for 2h. A solution of **LI-2b** (1.22 g, 6.15 mmol) and DMAP (751 mg, 6.15 mmol) in chloroform (5 mL) was added, and the mixture was stirred at RT for 16 h. After usual aqueous work-up and chromatographic purification, 2.02 g (67%) of pure **I-CI-NOPD16** was obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.39 (s, 3H), 2.88-2.95 (m, 4H), 3.69 (s, 2H), 3.84 (s, 3H), 4.38 (t, 2H, *J* = 6.3 Hz), 4.63 (t, 2H, *J* = 6.6 Hz), 6.67 (dd, 1H, *J* = 2.4, 8.7 Hz), 6.87 (d, 1H, *J* = 8.7 Hz), 6.96 (d, 1H, *J* = 2.1 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 8.4 Hz). MS (ES⁺) m/z: 539.2 [M+H]⁺, 560.79 [M+Na]⁺.

Example 96

Synthesis of NO-releasing prodrug of indomethacin (I-CI-NOPD18):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of indomethacin (3.01 g, 8.42 mmol) in THF (50 mL) at RT was added CDI (1.64 g, 10.10 mmol). After 1 h, **LI-5.TFA** (3 g, 8.42 mmol) was added at 0 °C, followed by TEA (5.9

mL, 42.1 mmol) and DMAP (0.6 g, 4.91 mmol). The reaction mixture was stirred at RT for 2 d. After usual aqueous work-up and chromatographic purification, 3.16 g (70%) of **I-C1-NOPD18** were obtained as yellow solid. ¹H NMR (CDCl₃, 300 MHz): δ 2.38 (s, 3H), 2.79 (t, 2H, J = 6.3 Hz), 2.86 (t, 2H, J = 6.9 Hz), 3.54 (q, 2H, J = 6.0 Hz), 3.66 (s, 2H), 3.83 (s, 3H), 4.61 (t, 2H, J = 6.6 Hz), 6.01 (bs, 1H), 6.71 (dd, 1H, J = 2.1, 9.0 Hz), 6.9 (dd, 2H, J = 3.3, 8.1 Hz), 7.49 (d, 2H, J = 8.4 Hz, 2H), 7.66 (d, 2H, J = 8.4 Hz). MS: m/z 538.10 [M+H]⁺, 560.1 [M+Na]⁺.

Example 97

Synthesis of NO-releasing prodrug of ketoprofen (I-C1-NOPD19):

- 10 This prodrug was synthesized as shown in Scheme 11, Method A according to the method described in Example 90, using as reagents ketoprofen (1.27 g, 5 mmol), CDI (1.21 g, 7.5 mmol) and **LI-2b** (1 g, 5 mmol). Yield: 0.6 g (51%). ¹H-NMR (300 MHz, CDCl₃): δ 1.55 (d, 3H, J = 7.0 Hz), 2.80-2.95 (m, 4H), 3.82 (q, 1H, J = 6.7 Hz), 4.35 (t, 2H, J = 6.1 Hz), 4.64 (t, 2H, J = 6.5 Hz), 7.40-7.85 (m, 9H). MS (ES⁺) m/z: 436.06 [M+H]⁺, 458.02 [M+Na]⁺.

Example 98

Synthesis of NO-releasing prodrug of ketoprofen (I-C1-NOPD20a):

- 20 This prodrug was synthesized as shown in Scheme 11, Method I. Thus, to a solution of the amide of ketoprofen (1.78 g, 7 mmol) in DCE (70 mL) was added oxalyl chloride (1.0 g, 8.4 mmol) at 0 °C and refluxed for 16 h. After cooling to RT, a solution of **LI-2B** (1.4 g, 7 mmol) in DCE (10 mL) was added and stirred for 20 h. After usual aqueous work-up and chromatographic purification, 0.6 g (17 %) of I-C1-NOPD20a was obtained as a pale yellow gum. ¹H NMR (CDCl₃, 300 MHz): δ 1.47 (d, 3H, J = 6.96 Hz), 3.00 (bs, 4H), 4.00 (q, 1H, J = 6.81 Hz), 4.39 (t, 2H, J = 6.21 Hz), 4.68 (bs, 2H), 7.47-7.77 (bs, 9H). MS: ES⁺ m/z 478[M+H]⁺, 477.15[M-H]⁺.

Example 99

Synthesis of NO-releasing prodrug of diclofenac (I-C1-NOPD22):

- 30 This prodrug was synthesized as shown in Scheme 11, Method B, using as reagents diclofenac (1.0 g, 3.378 mmol), **LI-2b** (0.68 g, 3.37 mmol), DMF (8 mL), DCC (0.835 g, 4.054 mmol) and DMAP (0.082 g, 0.675 mmol). Yield: 0.35 g (22 %). ¹H-NMR (300 MHz, CDCl₃): δ 2.91-3.04 (m, 4H), 3.85 (s, 2H), 4.42 (t, 2H, J = 6.6 Hz), 4.72 (t, 2H, J =

6.6 Hz), 6.56 (d, 1H, J = 8.1 Hz), 6.82 (s, 1H), 6.94-7.03 (m, 2H), 7.12-7.27 (m, 2H), 7.35 (d, 1H, J = 8.1 Hz). MS (ES⁺) m/z: 476.90 [M+H]⁺, 498.86 [M+Naf].

Example 100

Synthesis of NO-releasing prodrug of flurbiprofen (**I-C1-NOPD26**):

- 5 This prodrug was synthesized as outlined in Scheme 20. Thus, to a solution of **S20-I1** (0.8 g, 2.90 mmol) in THF (10 mL) and DMF (10 mL) was added the cesium salt of flurbiprofen (1.2 g, 3.19 mmol) and stirred at RT for 2 h. After usual aqueous work-up and chromatographic purification, 1.13 g (80 %) of **I-C1-NOPD26** was obtained as a light yellow semi solid. ¹H NMR (500 MHz, CDCl₃): δ 1.58 (d, 3H, J = 7.5 Hz), 2.88-2.94 (m, 4H), 3.88 (q, 1H, J = 7.0 Hz), 4.40 (t, 2H, J = 6.5 Hz), 4.64-4.68 (m, 4H), 7.14-7.54 (m, 8H). MS: m/z 501.1 [M+NH₄]⁺, 506.1 [M+Naf].
- 10

Example 101

Synthesis of NO-releasing prodrug of gabapentin ethyl ester (**I-A1-NOPD1**):

- 15 This prodrug was synthesized as shown in Scheme 12, Method A. Thus, to a stirred solution of diphosgene (0.88 mL, 7.37 mmol) in DCM (3 mL) at 0 °C was added drop-wise a solution of **LI-2a** (0.80 g, 3.68 mmol) & Hunig's base (1.92 mL, 11.85 mmol) in DCM (1 mL). The mixture was stirred at 0 °C for 30 min and concentrated. The residue was dissolved in DCM (4 mL) and treated with gabapentin ethyl ester hydrochloride (0.95 g, 4.05 mmol) & Hunig's base (1.39 mL, 8.05 mmol). The mixture was stirred at
- 20 RT for 3 h and concentrated. The residue, after usual aqueous work-up, gave 1.6 g (98 %) of **I-S12-I1**. ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 444 [M+H]⁺, 465.9 [M+Na]⁺.

- To a stirred solution of **I-S12-I1** (1.3 g, 2.94 mmol) in acetonitrile (8 mL) at RT was added silver nitrate (0.6 g, 3.52 mmol) portion-wise and stirred at RT for 2.5 h. After
- 25 filtration through celite, the filtrate was concentrated and the residue purified by column chromatography to afford 0.561 g (45 %) of prodrug **I-A1-NOPD1**. ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 425 (M+H)⁺, 447 (M+Na)⁺.

Example 102

Synthesis of NO-releasing prodrug of lamotrigine (**I-A1-NOPD3a** and **I-A1-NOPD3b**):

- 30 This prodrug was synthesized as shown in Scheme 12, Method B. Thus, to a suspension of lamotrigine (1 g, 3.90 mmol) in toluene (20 mL) at 120 °C was added drop-wise a

solution of the imidazolidine of **LI-2b** (1.4 g, 4.70 mmol) in THF (10 mL) and refluxed for 6 h. After usual aqueous work-up and chromatographic purification, 340 mg (20%) of **I-A1-NOPD-3a/b** was obtained. ¹H-NMR data is consistent with the expected structure. MS (ES)⁺ m/z: 481 (M+H)⁺.

5 Example 103

Synthesis of NO-releasing prodrug of nicotinic hydrazide (**I-A1-NOPD4**):

This prodrug was synthesized from nicotinic hydrazide (235 mg, 1.70 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.21 g (34%) of prodrug **I-A1-NOPD4**. ¹H-NMR (300 MHz, DMSO-d₆): δ 3.02 (t, 2H, J = 5.8 Hz), 3.10 (t, 2H, J = 6.1 Hz), 4.28 (t, 2H, J = 5.8 Hz), 4.76 (t, 2H, J = 6.1 Hz), 7.51-7.55 (dd, 1H, J = 4.8 Hz, 7.7 Hz), 8.17 (d, 1H, J = 7.8 Hz), 8.74 (d, 1H, J = 3.8 Hz), 8.98 (s, 1H), 9.44 (bs, 1H), 10.54 (bs, 1H). MS (EI)⁺ m/z: 363 [M+H]⁺.

Example 104

15 Synthesis of NO-releasing prodrug of lisinopril dimethyl ester (**I-A1-NOPD5**):

This prodrug was synthesized from lisinopril dimethyl ester hydrochloride (1.10 g, 2.56 mmol) according to the procedure described in Example 101 (see Scheme 12, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.76 g (67%) of prodrug **I-A1-NOPD5**. ¹H-NMR (300 MHz, CDCl₃): δ 1.49-1.54 (m, 2H), 1.93-2.07 (m, 8H), 2.12-2.28 (m, 1H), 2.64-2.68 (m, 2H), 2.91-3.0 (m, 4H), 3.18-3.25 (m, 3H), 3.42-3.47 (m, 1H), 3.52-3.55 (m, 2H), 3.69 (s, 3H), 3.73 (s, 3H), 4.28 (t, J = 6.3 Hz, 2H), 4.47-5.05 (m, 1H), 4.69 (t, J = 6.8 Hz, 2H), 5.22 (bt, 1H), 7.14-7.19 (m, 3H), 7.23-7.28 (m, 2H). MS (EI)⁺ m/z: 659 [M+H]⁺.

Example 105

25 Synthesis of NO-releasing prodrug of omeprazole (**I-A1-NOPD6**):

This prodrug was synthesized as shown in Scheme 12, Method B. To an ice-cold solution of diphosgene (0.3 mL, 2.48 mmol) in toluene at 0 °C, was added a mixture of **LI-2b** (0.5 g, 2.51 mmol) and TEA (0.42 mL, 3.0 mmol) in toluene (3 mL) and stirred for 2 h. In a separate flask, omeprazole (0.867 g, 2.50 mmol) was dissolved in THF (5 mL), cooled to 0 °C and NaH (0.059 g, 2.5 mmol) was added. The mixture was stirred for 30 min, the above reaction mixture was added dropwise to it and stirred for 2 h. After usual aqueous

work-up and chromatographic purification, 0.23 g (20 %) of **I-A1-NOPD6** was obtained as a reddish-yellow gum. ¹H-NMR: (CDCl₃, 300 MHz): 2.21 (s, 3H), 2.36 (s, 3H), 2.93-3.05 (m, 2H), 3.19-3.28 (m, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 4.70-4.87 (m, 6H), 7.10-7.80 (m, 3H), 8.10 (s, 1H). MS: ES⁺ m/z 571 (M+H)⁺, 593 (M+Na)⁺.

5 **Example 106**

Synthesis of NO-releasing prodrug of hydralazine (**I-A1-NOPD7**):

This prodrug was synthesized from hydralazine hydrochloride (0.99g, 5.01mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.8 g
10 (41%) of prodrug **I-A1-NOPD7**. ¹H-NMR (300 MHz, CDCl₃): δ 2.95-3.06 (m, 4H), 4.43 (t, 2H, J = 6.35Hz), 4.69 (t, 2H, J = 6.7 Hz), 7.57 (m, 1H), 7.63-7.71(m, 2H), 8.16 (s, 1H), 8.29 (d, 1H, J = 7.6 Hz). MS (ES⁺) m/z: 386.05 (M+H)⁺.

Example 107

Synthesis of NO-releasing prodrug of amlodipine (**I-A1-NOPD8**):

15 This prodrug was synthesized from amlodipine (1.67 g, 4.09 mmol) according to the procedure described in Example 109 (see Scheme 12, Method B). After usual workup, the crude product was purified by column chromatography to afford 1.33 g (61%) of **I-A1-NOPD8**. ¹H-NMR (300 MHz, CDCl₃): δ 1.18 (t, 3H, J = 7.1 Hz), 2.36 (s, 3H), 2.93-2.99 (m, 4H), 3.47 (bs, 2H), 3.61-3.64 (m, 5H), 4.04 (q, 2H, J = 7.1 Hz), 4.35 (bt, 2H),
20 4.68-4.74 (m, 4H), 5.0 (bs, 1H), 7.13-7.36 (m, 4H). MS (ES⁺) m/z: 634.14 (M+H)⁺, 656.83 (M+Na)⁺; (ES⁻) m/z: 631.94 (M-H)⁺.

Example 108

Synthesis of NO-releasing prodrug of levetiracetam (**I-A2-NOPD1a**):

25 This prodrug was synthesized from levetiracetam (1.0 g, 5.87 mmol) according to the procedure generally described in Example 82 (see Scheme 13, Method A). After usual workup and chromatographic purification, the product was further purified by preparative HPLC to afford 728 mg (31%) of prodrug **I-A2-NOPD1a**. ¹H-NMR was consistent with the expected structure. MS (ES)⁺ m/z: 396.1 [M+H]⁺, 418.1 [M+Na]⁺, (ES)⁻ m/z: 394.1 [M-H]⁻.

30 **Example 109**

Synthesis of NO-releasing prodrug of valdecoxib (**I-A3-NOPD1a**):

This prodrug was synthesized as shown in Scheme 13, Method B. Thus, to a cold suspension of sodium hydride (271 mg, 6.81 mmol) in THF (7 mL) was added drop-wise a solution of valdecoxib (1.78 g, 5.68 mmol) in THF (15 mL) and stirred at RT for 2 h. A solution of the imidazolidine of **LI-2b** (2.0 g, 6.81 mmol) in THF (15 mL) was added and stirred at room temperature for 18 h. The reaction mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 976 mg (32 %) of prodrug **I-A3-NOPD1a**. ¹H-NMR data is consistent with the expected structure. MS (ES)⁺ m/z: 538 [M-H]⁺.

Example 110

10 Synthesis of NO-releasing prodrug of celecoxib (**I-A3-NOPD2a**):

This prodrug was synthesized from celecoxib (6.62 g, 17.35 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 1.55 g (15%) of prodrug **I-A3-NOPD2a**. ¹H-NMR (300 MHz, CDCl₃): δ 2.38 (s, 3H), 2.84-2.98 (m, 4H), 4.34 (t, 2H, J = 6.45 Hz), 4.63-4.71 (m, 2H), 6.74 (s, 1H), 7.09-7.25 (m, 4 H), 7.51 (d, 2H, J = 6.8 Hz), 8.02 (d, 2H, J = 6.8 Hz). MS (ES)⁺ m/z: 606.87 [M + H]⁺, 628.93 [M + Na]⁺; (ES)⁺ m/z: 604.88 [M-H]⁺.

Example 111

20 Synthesis of NO-releasing prodrug of paracetamol (**I-H1-NOPD1**):

This prodrug was synthesized as shown in Scheme 14, Method B. Thus, to a solution of paracetamol (2.0 g, 13.24 mmol) in THF (20 mL) was added CDI (2.36 g, 14.57 mmol) and the mixture was stirred at RT for 3 h. To this was added a solution of **LI-2b** (1.21 g, 6.62 mmol), followed by DMAP (0.802 g, 6.622 mmol) and stirred overnight at RT. The mixture was quenched with water and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 0.3 g (6%) of prodrug **I-H1-NOPD1**. ¹H-NMR data is consistent with the expected structure. MS (CI)⁺ m/z: 376 [M+H]⁺.

Example 112

30 Synthesis of NO-releasing prodrug of paracetamol (**I-H1-NOPD2a**):

This prodrug was synthesized as shown in Scheme 14, Method D. Thus, to a solution of chlorocarbonyl isocyanate (0.701g, 6.622 mmol) in benzene (5 mL) at 0 °C was added a solution of paracetamol (1 g, 6.622 mmol) and stirred at 0 °C for 1 h. To this was added a

solution of **LI-2b** (1.21 g, 6.622 mmol) and TEA (1 mL) in THF (5 mL), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 90 mg (3%) of prodrug **I-H1-NOPD2a** was obtained. ¹H-NMR data was consistent with the expected structure. MS: (ES)⁻ m/z: 418 [M-H]⁻.

5 **Example 113**

Synthesis of NO-releasing prodrug of paracetamol (**I-H1-NOPD3**):

This prodrug was synthesized from paracetamol (2.0 g, 13.24 mmol) according to the procedure described in Example 122 (see Scheme 14, Method C). After usual workup, the crude product was purified by column chromatography to afford 1.0 g (20%) of
10 prodrug **I-H1-NOPD3**. ¹H-NMR (500 MHz, CDCl₃): δ 2.11 (s, 3H), 2.91 (t, 2H, J = 6.5 Hz), 3.06 (t, 2H, J = 6.5 Hz), 3.49 (t, 2H, J = 6.5 Hz), 4.75 (t, 2H, J = 6.5 Hz), 7.05 (d, 2H, J = 9.0 Hz), 7.54 (d, 2H, J = 9.0 Hz). MS (ES)⁺ m/z: 376 [M+H]⁺, 393 [M+NH₄]⁺, 397 [M+K]⁺.

Example 114

15 Synthesis of NO-releasing prodrug of metronidazole (**I-H1-NOPD6**):

This prodrug was synthesized in two steps as shown in Scheme 14, Method C.

Step 1: To a suspension of metronidazole (5 g, 29.22 mmol) in chloroform (100 mL) was added CDI (5.21 g, 32.2 mmol) and stirred overnight at RT. The reaction mixture, after usual aqueous work-up, gave 7.66 g (98 %) of the imidazolide intermediate. ¹H-NMR
20 data was consistent with the expected structure. MS (ES)⁺ m/z: 266.1 [M + H]⁺.

Step 2: To a mixture of **LI-5.TFA** (2.68 mmol) and TEA (1.08 g, 10.72 mmol) in DCM (10 mL) at 0 °C was added the imidazolide of metronidazole (0.78 g, 2.95 mmol) and stirred at RT for 48 h. The reaction mixture was quenched with water and extracted with DCM. After usual aqueous work-up and chromatographic purification, 50 mg (4.3%) of
25 **I-H1-NOPD6** was obtained. ¹H-NMR (500 MHz, CDCl₃): δ 2.50 (s, 3H), 2.80 (t, 2H, J = 6.3 Hz), 2.96 (t, 2H, J = 6.6 Hz), 3.47-3.50 (m, 2H), 4.41 (t, 2H, J = 5.1 Hz), 4.58 (t, 2H, J = 5.1 Hz), 4.70 (t, 2H, J = 6.6 Hz), 7.96 (s, 1H). MS (ES)⁺ m/z: 395.99 [M+H]⁺.

Example 115

Synthesis of NO-releasing prodrug of budesonide (**I-H1-NOPD9**):

30 This prodrug was synthesized from budesonide (0.5 g, 1.16 mmol) according to the procedure described in Example 122 (see Scheme 14, Method C). After usual workup,

the crude product was purified by column chromatography to afford 0.25 g (33%) of prodrug **I-H1-NOPD9**. ^1H -NMR data was consistent with the expected structure. MS (ES) $^+$ m/z: 655 [M+H] $^+$.

Example 116

5 Synthesis of NO-releasing prodrug of 4-Hydroxy-TEMPO (**I-H1-NOPD10**):

A solution of **LI-2b** (0.20 g, 1.20 mmol) and CDI (0.195 g, 1.20 mmol) in chloroform (5 mL) was stirred at RT for 2 h, which was followed by the addition of 4-hydroxy-TEMPO (0.173 g, 1.00 mmol) and DMAP (0.122 g, 1.00 mmol). The mixture was refluxed for 2 d, then purified by column chromatography to afford 110 mg (27 %) of **I-H1-NOPD10** as a red oil. MS: EI $^+$ m/z 398 [M+H] $^+$, 420 [MH-Na] $^+$.

Example 117

Synthesis of NO-releasing prodrug of edaravone (**I-H1-NOPD11**):

To a solution of edaravone (0.87 g, 5 mmol) in acetonitrile was added KF-Al₂O₃ (66 g) and, under thorough mixing, **LI-3a** (2.8 g, 10 mmol) was added. The mixture was agitated for 20 h. After usual aqueous work-up and chromatographic purification, 70 mg (4%) of the intermediate bromide was obtained as a reddish-yellow oil. ^1H NMR (CDCl₃, 500 MHz): δ 2.28 (s, 3H), 3.00-3.10 (m, 4H), 3.59 (t, 2H, J = 8 Hz), 4.34 (t, 2H, J = 6.5 Hz), 5.5 (s, 1H), 7.4 (t, 2H, J = 1 Hz), 7.69 (t, 3H, J = 1 Hz). MS: ES $^+$ m/z 375 [MH-H] $^+$, 397.0 [MH-Na] $^+$.

20 To a solution of the above bromide (0.05 g, 0.134 mmol) in acetonitrile (1.5 mL) was added AgNO₃ (0.027 g, 0.160 mmol) and stirred for 20 h. After usual aqueous workup and purification, 0.025 g (53 %) of **I-H1-NOPD11** was obtained as a brown gum. ^1H NMR (CDCl₃, 500 MHz): δ 2.28 (s, 3H), 2.90 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.5 Hz), 4.33 (t, 2H, J = 6.0 Hz), 4.63 (t, 2H, J = 6.5 Hz), 5.5 (s, 1H), 7.60-7.63 (bs, 2H), 7.65-7.67 (bs, 3H). MS: ES $^+$ m/z 356 [MH-H] $^+$.

Biological Example 1:**Screening of prodrugs and mutual prodrugs of anticonvulsants:**

Most of the prodrugs and mutual prodrugs of anticonvulsants described in this invention were evaluated at National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Health (NIH), under their Antiepileptic Screening Program (ASP).

Test 1 is an initial screening for anticonvulsant activity in the Maximal Electroshock Test (MES) and Subcutaneous Metrazol Seizure Threshold Test (scMET) models combined with an initial assessment of toxicity (TOX) in mice via i.p. injection (see further explanation below). The data for each condition is presented as N/F, where N = number of animals protected from seizure and F = number of animals tested. For test of toxicity, N = number of animals displaying toxic effects and F = number of animals tested. Any deaths occurring during the test were recorded.

Maximal Electroshock Test (MES): The MES is a model for generalized tonic-clonic seizure and provides an indication of a compound's ability to prevent seizure spread when all neuronal circuits in the brain are maximally active. These seizures are highly reproducible and electro-physiologically consistent with human seizures. For all tests based on MES convulsions, 60 Hz of alternating current (50 mA in mice) is delivered for 2s by corneal electrodes, which have been primed with an electrolyte solution containing an anesthetic agent (0.5% tetracaine hydrochloride). Mice were tested at various intervals following doses of 30, 100 and 300 mg/kg of test compound given by i.p. injection of a volume of 0.01 mL/g. Other doses can be used if indicated by previously known pharmacology. An animal is considered "protected" from MES-induced seizures upon abolition of the hind-limb tonic extensor component of the seizure.

Subcutaneous Metrazol Seizure Threshold Test (scMET): Subcutaneous injection of the convulsant metrazol produces clonic seizures in laboratory animals. The scMET test detects the ability of the test compound to raise the seizure threshold of an animal and thus protect it from exhibiting a clonic seizure. Animals were pretreated with various doses of the test compound given by i.p. injection. At the previously determined

Time to Peak Effect (TPE) of the test compound, the dose of metrazol which will produce convulsions in 97% of animals (CD_{97} : 85 mg/kg in mice) was injected into a loose fold of skin in the midline of the neck. The animals were placed in isolation cages to minimize stress and observed for the next 30 minutes for the presence or absence of a seizure. An episode of clonic spasms, approximately 305 seconds, of the fore and/or hind limbs, jaws, or vibrissae is taken as the end point. Animals which do not meet this criterion were considered protected.

Acute Toxicity - Minimal Motor Impairment (MMI): To assess a compound's undesirable side effects (toxicity), animals were monitored for overt signs of impaired neurological or muscular function. In mice, the rotorod procedure is used to disclose minimal muscular or neurological impairment. When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal can maintain its equilibrium for long periods of time. The compound is considered toxic if the animal falls off this rotating rod three times during a 1-min period. In addition to MMI, animals may exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of placing response and changes in muscle tone.

Compounds that were active in Test 1 (mice i.p.) were further screened in Test 2 (rat p.o.). Compounds retaining activity in Test 2 (rat p.o.) were selected for secondary evaluation (i.e., Test 3, Rat P.O. quantification) as explained below:

Secondary Evaluation: All quantitative *in vivo* anticonvulsant/toxicity evaluations of the active compounds were conducted at compound's time of peak pharmacodynamic activity (TPE). Groups of at least 8 rats received various doses of the candidate compound until at least two points were established between the limits of 100 percent protection or toxicity and zero percent protection or minimal toxicity. The 95 percent confidence limits, slopes of the regression lines and standard errors of the slopes were calculated for each quantitative determination. Rats received test compounds orally.

Test 1 screening results are presented in Table 1. Compound **I-CA-MPD24** was active in both MES and scMET models and was shown to be non-toxic. However, some compounds were active in both MES and scMET models and were also shown to be

toxic. The compounds (i.e., I-A1-PD4, I-AA-MPD12, I-CA-MPD23, I-A1-PD5, I-A1-NOPD3, I-CA-MPD24, **I-A1-PD15**, I-CA-MPD25, and **I-AA-MPD11**) that are shown to be active in MES but showed no or mild toxicity were selected for Test 2 screening and those results are presented in Table 2.

- 5 Three of the compounds (i.e., I-A1-PD4, I-AA-MPD12, and **I-A1-NOPD3**) were considered for secondary evaluation, where quantification of their antiepileptic activity and neurotoxicity in rats (p.o.) was carried out. This secondary evaluation determines the time to peak effect (TPE), neurotoxicity, median effective dose (ED50) and biological response. The 95% confidence interval, the slope of the regression line, and the standard error are then calculated. The results of secondary evaluation (Test 3) are presented in
10 Tables 3A and 3B.

Table 1: Primary Screening (Test 1) data for Anticonvulsant Activity and Neurotoxicity in Mice (test compound administered i.p.)

Compd	MES ^{a,b}		ScMET ^{a,c}		Rotorod Toxicity ^{a,d}	
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
I-A1-PD7	+(1/1)	-	+(1/1) ^e	-	+(2/4) ^d	-
I-A1-PD8	++ (2/3)	-	-	-	-	-
	+(1/1)	+(1/1)	+(1/1)	-	+(4/4) ^f	-
I-A1-PD4	-	+++ (1/1)	-	-	-	-
	++ (1/7)	++ (3/3)	-	-	-	-
	+(2/5)	+(1/1)	-	-	-	-
I-AA-MPD12	-	++ (3/3)	-	-	-	-
	nd	++ (1/3) ^g	nd	nd	nd	nd
	-	+(1/1)	-	-	-	-
I-CA-MPD23	-	++ (1/3) ^h	-	-	-	-
	-	+(1/3)	-	-	-	-
I-A1-PD13	+(1/1)	-	+(1/1)	-	+(1/4)	-
I-A1-PD5	+(1/1)	-	+(3/5)	-	+(3/4) ⁱ	-
I-A1-PD6	+(1/1)	-	+(1/1)	-	+(4/4) ⁱ	-
I-A1-PD10	-	-	-	-	++ (8/8) ^j	nd

I-AA-MPD13	-	-	+(1/1)	-	+(4/4) ^j	-
I-A1-NOPD1	++ (1/3) ^k +(1/1)	- -	- +(1/1)	- -	- +(4/4) ⁱ	- -
I-A1-NOPD3	- -	++ (1/3) +(1/1)	++ (1/1) ^l -	- -	+++ (1/4) -	- -
I-CA-MPD24	- - -	++ (3/3) ++ (3/3) ^h ++ (3/3) ^m	- - -	- - + (1/1) ^l	- - -	- - -
I-A1-PD15	+ (1/1) -	++ (2/3) +(1/1)	- -	- -	- -	- -
I-CA-MPD25	+ (1/1) -	++ (2/3) +(1/1)	- -	- -	- -	- -
I-AA-MPD11	- +(1/1)	++ (3/3) +(1/1)	- -	- -	- +(1/4)	- -

^aKey: +++ = activity or toxicity at 30 mg/kg, ++ = activity or toxicity at 100 mg/kg, + = activity or toxicity at 300 mg/kg, - = no activity or no toxicity at 300 mg/kg.

^bMaximal electroshock seizure test. ^cSubcutaneous pentylenetetrazol seizure test.

5 ^dNeurological toxicity (number of animals exhibiting toxicity/number of animals tested). ^e(number of animal protected/number of animal tested), nd = not determined.

^fLoss of righting reflex. ^gAt 6 hours after dosing. ^hAt 2 hours after dosing. ⁱUnable to grasp rotorod. ^jDeath. ^kAt 0.25 hours after dosing. ^lMyoclonic jerks. ^mAt 6 hours after dosing.

10 Table 2: Screening (Test 2) data for Anticonvulsant Activity and Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose (mg/kg)	Time (h)	MES ^{a,b}	Toxicity ^{c,d}
I-A1-PD4	30	0.50	0/4	0/4
		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-AA-MPD12	30	0.50	0/4	0/4
		1.00	0/4	0/4
		2.00	1/4	0/4
		4.00	3/4	0/4
I-CA-MPD23	150	2.00	4/4	0/4
		4.00	4/4	0/4
		6.00	4/4	0/4
		8.00	4/4	0/4
I-A1-PD5	50	0.50	0/4	0/4
		1.00	0/4	0/4
		2.00	1/4	0/4
		4.00	1/4	0/4
I-A1-NOPD3	30	0.50	0/4	0/4
		1.00	2/4	0/4
		2.00	1/4	0/4
		4.00	4/4	0/4
I-CA-MPD24	30	0.50	0/4	0/4
		1.00	2/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-A1-PD15	30	0.50	0/4	0/4
		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-CA-MPD25	30	0.50	0/4	0/4
		1.00	3/4	0/4

		2.00	4/4	0/4
		4.00	2/4	0/4
I-AA-MPD11	30	0.50	0/4	0/4
		1.00	2/4	0/4
		2.00	1/4	0/4
		4.00	4/4	0/4

^aMaximal electroshock seizure test. ^b(number of animal protected/number of animal tested). ^cNeurological toxicity. ^d(number of animals exhibiting toxicity (i.e., atoxia)/number of animals tested).

- 5 Table 3A: Screening (Test 3) data for Anticonvulsant Activity (Time to Peak Effect) and Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose (mg/kg)	Time (h)	Time to Peak Effect		Toxicity ^{d,e} (mg/kg)
			MES ^{a,b}	ScMET ^{b,c} (50 mg/kg)	
I-A1-PD4	10	4.0	4/4		
		6.0	3/4		
		8.0	2/4		
		24	0/4		
	30	0.25	2/4	1/4 ^f	0/4 (100)
		0.5	2/4	0/4	0/4 (100)
		1.0	2/4	2/4	0/4 (100)
		2.0	2/4	1/4 ^g	0/4 (100)
		4.0	4/4	0/4	
I-AA-MPD12	15	6.0	2/4		
		8.0	1/4		

	30	0.5	0/4		
		1.0	0/4	1/4	0/4 (50)
		2.0	1/4	0/4	0/4 (50)
		4.0	3/4	0/4	0/4 (50)
		6.0	4/4	1/4	0/4 (50)
		8.0	4/4	2/4	0/4 (50)
		24	2/4	0/4	0/4 (50)
		8.0			1/8 (100) ^h
I-A1-NOPD3	30	0.25			0/8 (500)
		0.5			0/8 (500)
		1.0			0/8 (500)
		2.0	1/4	0/4	0/8 (500)
		4.0	3/4	0/4	0/8 (500)
		6.0	3/4	1/4	1/8 (500)
		8.0	4/4	3/4	0/8 (500)
		24	3/4	1/4	

^aMaximal electroshock seizure test. ^b(number of animal protected/number of animal tested).

^cSubcutaneous pentylenetetrazole seizure test. ^dNeurological toxicity.

^e(number of animals exhibiting toxicity (i.e., atoxia)/number of animals tested).

- 5 ^fDeath following continuous seizure. ^sPopcorn effect and continuous seizure activity. ^hMild ataxia only.

Table 3B: Screening (Test 3) data for Anticonvulsant Activity (ED₅₀ and Biological Response and ED₅₀) in Rats (test compound administered p.o.)

Compd	ED 50 Values and Biological Response					
	Time (h)	Dose (mg/kg)	MES ^{a,b}	ED ₅₀	95% Confidence Interval Low/High	Slope/Std.Er

I-A1-PD4	4	1.9	0/8	6.55	3.56/10.72	2.27/0.63
		3.8	4/8			
		7.5	4/8			
		15	7/8			
		30	7/8			
I-AA-MPD12	6	7.5	0/8	17.1	9.98/25.8	3.2/0.95
		15	5/8			
		30	7/8			
		60	7/8			
I-A1-NOPD3	8	3.8	3/8	10.1	2.99/17/44	1.61/3.15
		7.5	3/8			
		15	4/8			
		30	9/12			
		60	8/8			

^aMaximal electroshock seizure test. ^b(number of animal protected/number of animal tested).

I-A1-PD4 is a simple prodrug of lamotrigine. For this prodrug, ED₅₀ for the MES model was determined to be 6.55 mg/kg and the time to peak effect was found to be 4.0 h after drug administration at doses of 10 as well as 30 mg/kg. This compound has shown moderate protection in scMET models where one out of four animals were protected at 0.25 h and 2.0 h period and two out of four animals were protected at 1.0 h after administration of the drug at a dose of 50 mg/kg. For the toxicity analysis, none of the animals given 100 mg/kg showed signs of toxicity.

I-AA-MPD12 is a mutual prodrug of lamotrigine and gabapentin ethyl ester. For this compound, ED₅₀ for the MES model was found to be 17 mg/kg and the time to peak effect was found to be 6.0-8.0 h at a dose of 30 mg/kg and indicated a significant extension protection (2 out of 4 animals were still protected) at 24 h after drug administration. Surprisingly, this compound, although less potent than lamotrigine, has exhibited significant extension in the duration of protection. At 50 mg/kg, none of the animals exhibited toxicity. However, at 100 mg/kg, one of eight animals exhibited mild ataxia.

I-A1-NOPD3 is a NO-releasing prodrug of lamotrigine. For this prodrug, ED50 for the MES model was determined to be 10.1 mg/kg and the time to peak effect was found to be at 8.0 h at a dose of 30 mg/kg and revealed a significant extension of protection (3 out of 4 animals were still protected) even at 24 h after drug administration. Surprisingly, this prodrug, although less potent than its parent drug, has exhibited significant extension in the duration of protection. At 50 mg/kg, this compound has also exhibited significant protection (3 out of 4 animals were protected at 8 h after drug administration) in scMET rat model. For the toxicity analysis, only one in eight animals exhibited toxicity at 6.0 h time point at a dose of 500 mg/kg. At other time points (i.e., 0.25 h, 0.5 h, 1.0 h, 2.0 h, 4.0 h, 8.0 h after drug administration), none of the animals (0/8) exhibited any significant toxicity at the high dose of 500 mg/kg.

Biological Example 2:

The pharmacological experiments on NO-releasing aspirin prodrugs were carried out by following the procedures described herein:

15 Animals and Procedures:

Male or female Sprague-Dawley rats weighing 150-200 g were used in the study. The rats were fed normal standard laboratory chow and maintained under standard conditions (room temperature of 22 ± 2 °C; 50 ± 10 % relative humidity; artificial light 06:00 to 18:00). All experimental procedures mentioned below are approved by institutional animal research committees and were performed in accordance with standard guidelines for the treatment of animals.

Sample preparation and standard curve:

HPLC: Waters Alliance analytical HPLC equipped with 2996 PDA detector and Empower software were used to analyze the samples.

25 HPLC Column: Waters X-Terra RP-18 analytical column, 150 X 3.9 mm, 5 μ .

HPLC Method: Flow: 1 mL/min, detector set at 210 nm and at Maxplot (210-400 nm range). Solvent A: Acetonitrile; Solvent B: 0.1% TFA in water. Elution method: A linear gradient of 0-100% A.

Plasma samples were processed by transferring 75 μ L quantity of blood into a test tube containing 250 μ L acetonitrile, vortex-mixed and centrifuged at 1000 g for 5 min. 200 μ L of supernatant was then taken and diluted to 2 times with acetonitrile. 100 μ L of

the sample was injected into HPLC for analysis. Salicylate standard curves were generated using acetonitrile as solvent in the working range of 1-100 µg/ml.

Pharmacokinetic parameters were calculated using WinNonlin software (4.1 version). C_{max}, T_{max}, AUC 0-24, AUC 0-infinity, and T_{y2} characterized and each curve generated following oral treatment.

In Vitro Plasma stability:

The rationale is that the prodrugs would be hydrolyzed in-vivo before, during or after absorption to release the corresponding free drugs. Therefore, we tested whether the test compounds (I-C1-NOPD6, I-C1-NOPD4, I-C1-NOPD5A) released parent drug in rat plasma at 37 °C after 30 minutes incubation. The compounds were extracted back into acetonitrile with rigorous vortex. The results suggested that all prodrugs tested except I-C1-NOPD6 were found to be converting to the expected metabolite (salicylate) of the parent drug (aspirin) as revealed by HPLC analysis. Even aspirin was completely metabolized to salicylate after 30 minutes of incubation with rat plasma indicating that all the test compounds released aspirin, which in turn converted into salicylate.

Pharmacokinetic studies:

The oral pharmacokinetics of the test compounds, I-C1-NOPD6, I-C1-NOPD4, I-C1-NOPD5A and I-C1-NOPD5B was done in rats and the release profiles of salicylate from these compounds were analyzed by HPLC and the results were presented in Figure 1 and Table 4. Overnight fasted rats were fed with 35 mg/kg equivalent doses of aspirin and test compounds. Blood was collected from orbital plexus of test animals at various time points up to 24 hrs. As shown in Figure 1, the test compounds I-C1-NOPD4 and I-C1-NOPD5B indicated unexpected drug release profiles wherein the salicylate is released in a sustained and controlled manner starting from 1 hour through 12 hours. For I-C1-NOPD5B, the plasma salicylate concentration was maintained between 50 and 75 µg/ml during this extended period of over 11 hours. This kind of plasma concentrations of the drug can result in significant extension of duration of action. For I-C1-NOPD4 also, the plasma salicylate concentration was maintained between 35 and 50 µg/mL during an extended period of over 11 hours. Although aspirin absorption (Figure 1) was highest during 0.5 - 6.0 hrs (during which period much of the damage to the gastrointestinal tract

of the subject occurs due to high concentrations of the drug), plasma salicylate concentration for aspirin and I-C1-NOPD4 were comparable during the period from 8 through 24 hours. Such sustained release profile of active drug from the prodrug is expected to cause negligible or insignificant gastrointestinal damage as the plasma concentration of the drug never reaches to the toxic levels. Similar release profile was observed with I-C1-NOPD5A but for a shorter period of time. Unexpectedly, we have also observed as recorded in Table 4, nearly equal drug AUC values for aspirin and I-C1-NOPD5B (i.e., 923.63 ± 182.08 for aspirin vs 951.98 ± 11.58 for I-C1-NOPD5B) which indicates that the prodrug is as bioavailable as its parent drug, but prodrug does not cause gastric damage. Surprisingly, neither the prodrug nor the salicylate was found in the plasma of the animals fed with I-C1-NOPD6 (data not included in the graph) at any point of time tested, the reasons for which are not known.

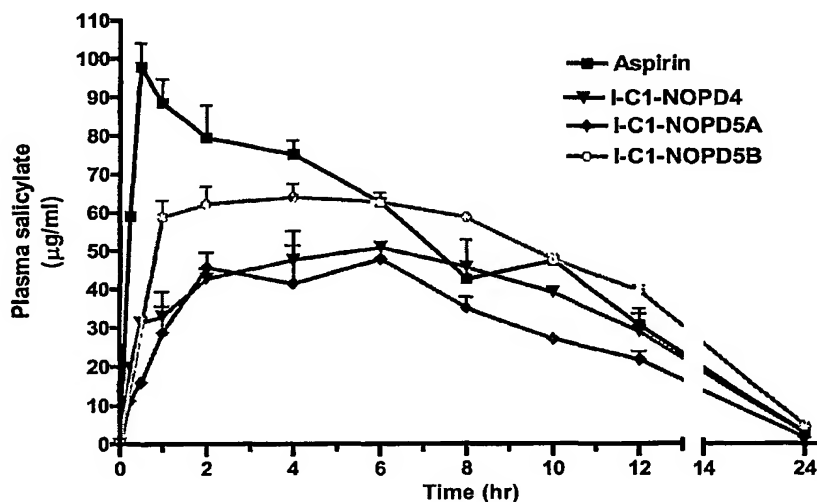


Figure 1. Plasma salicylate profile of aspirin and its NO-releasing prodrugs. The data values are expressed as Mean \pm S.E.M, $n=3-4$ animals. The data values at time points 6 and 10 hours is an average from two animals only.

Table 4. Comparison of pharmacokinetic parameters of aspirin and its nitro derivatives

Parameters*	Aspirin	I-C1-NOPD4	I-C1-NOPD5A	I-C1-NOPD5B
Cmax ($\mu\text{g/mL}$)	98.67 ± 12.64	53.24 ± 6.39	50.14 ± 10.12	66.08 ± 3.31
Tmax (h)	0.50 ± 0.00	4.66 ± 0.57	3.00 ± 0.57	4.00 ± 0.81

AUC _{0-24h} (h.µg/ml)	905.84 ± 173.14	749.36 ± 69.38	557.80 ± 97.65	922.89 ± 12.50
AUC _{0-α} (h.µg/ml)	923.63 ± 182.08	772.17 ± 75.68	565.30 ± 96.78	951.98 ± 11.58
Tin (h)	3.56 ± 0.42	3.98 ± 0.25	3.35 ± 0.32	4.14 ± 0.24

*The data values are mean ± SEM, *n* = 3-4

Ulcerogenic activity:

Gastrointestinal ulceration is a serious side effect associated with NSAIDs. The clinical uses of potent NSAIDs are greatly limited by its gastrointestinal toxicity. We tested ulcerogenic potential of the test compounds, I-C1-NOPD6, I-C1-NOPD4, I-C1-NOPD5A, and I-C1-NOPD5B in rats. Overnight fasted rats were given orally 100 mg/kg equivalent doses of aspirin and prodrugs (in the case of I-C1-NOPD5A and I-C1-NOPD5B, 200 mg/kg equivalent doses were administered). The animals were sacrificed at 3 hours after drug administration. Stomachs of treated rats were separated, perfused with 10 ml of 2 % formalin, and then cut open over the greater curvature. The severity of the mucosal damage was then assessed on the basis of size (area) of the observed ulcers under surgical microscope with a square grid as per the established procedure (Takeuchi et al., J. Pharmacol. Exp. Ther. 1998, 286 (1), 115-121). Interestingly, none of the animals treated with the test compounds showed any signs of development of ulcers. However, severe haemorrhagic lesions (Mean ± S.E.M.: 2.7 ± 0.9 mm²) were seen in aspirin treated rats.

Anti-inflammatory activity:

Anti-inflammatory activity of test compounds was measured in carrageenan-induced rat paw edema model (Takeuchi et al., J. Pharmacol. Exp. Ther. 1998, 286 (1), 115-121). The activity of aspirin and test compounds (75 mg/kg equivalent dose of aspirin) is shown in Table 5. Aspirin at 75 mg/kg, p.o. exhibited anti-inflammatory activity from 1 hr through 6 hr with peak maximal activity at 4 hr. I-C1-NOPD4 showed significant activity during the first two hours after drug administration but its activity was not as good as that of aspirin from 2 hr through 6 hr. Surprisingly, I-C1-NOPD5A showed negligible anti-inflammatory activity at any time point tested (data not incorporated). We have not yet evaluated I-C1-NOPD5B in this efficacy test.

Table 5

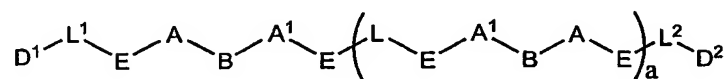
Compound	Rat paw edema (% inhibition)			
	Mean \pm SEM, n = 6			
	1 hour	2 hour	4 hour	6 hour
Aspirin	31.0 \pm 7.2	52.5 \pm 3.4	60.7 \pm 6.9	42.8 \pm 6.9
I-C1-NOPD4	42.4 \pm 13.3	44.9 \pm 12.9	24.3 \pm 7.7	8.6 \pm 5.1

The results indicate the following:

1. Sustained release of the active drug over a period of 10-11 hours, which is good for twice daily dosage regimen, and
2. Exceptional gastrointestinal safety even at high equivalent doses of prodrugs compared to aspirin, which caused severe ulcers at equivalent doses.

We claim:

1. A compound of formula (I) or pharmaceutically acceptable salts thereof:



Formula (I)

wherein,

a is 0-2;

B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_c$, S-S, S-S=O, S-SO₂ or S-S=NH;

b is 1-6; c is 1-1000;

A and A¹ independently represent a bond, $(CH_2)_d$, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

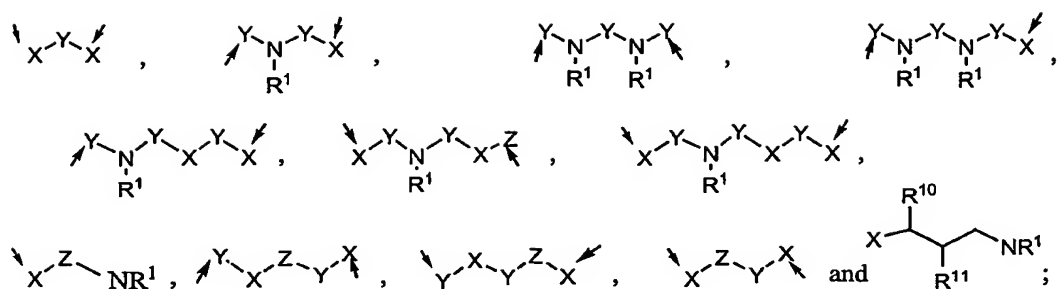
d is 1-8;

D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OCC(=O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹CC=O)NHR¹ and -N(R¹SO₂)NHR¹;

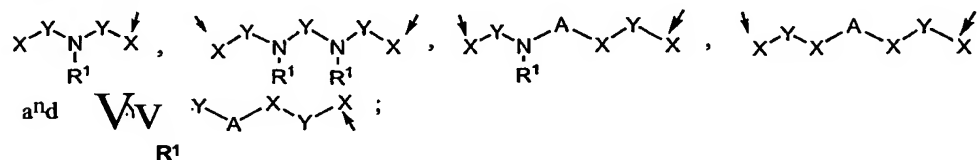
D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, NO₂, NONOate or any other nitric oxide-releasing group or molecule, a group or molecule comprising one or more of water-solubilizing functional groups, a polymer or an amino acid;

E independently represents CH₂ or a bond;

L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:



L is R¹² or a group with bonding in any direction, independently selected from the group consisting of:



X independently represents a bond, C, O, S, or NR¹;

Y independently represents a bond, C=O, C=S, S=O, SO₂, P(O)XR¹, or (CH₂)_d; wherein d is as defined;

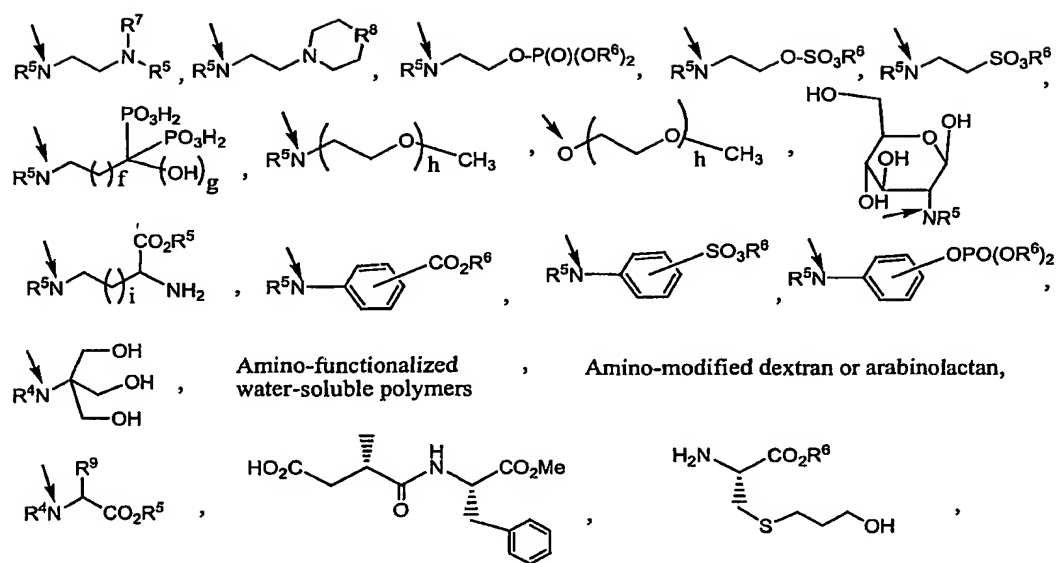
Z independently represents a bond, or (CH₂)_j; wherein, j is 1-4;

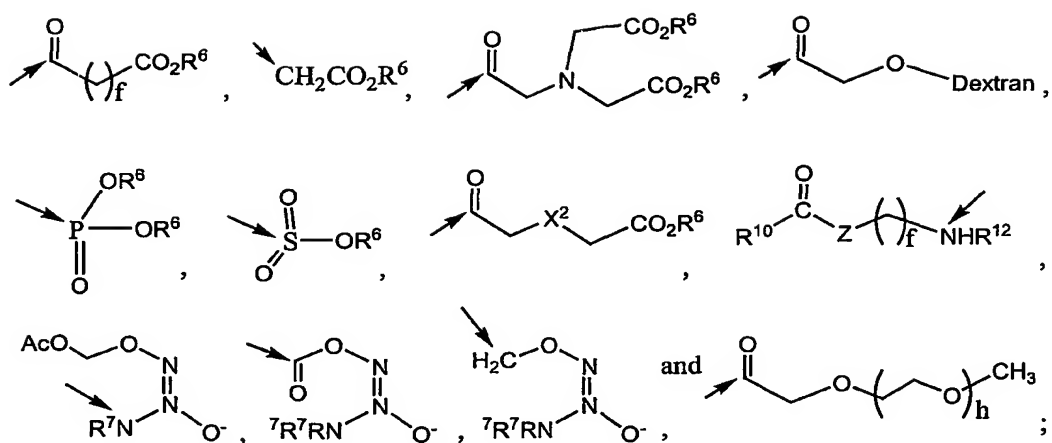
R¹ independently represents a bond, H, (d-Cs)alkyl, substituted(Ci-Cs)alkyl, (C₅-C₁₄)aryl, aralkyl or M⁶⁺;

R² independently represents H, NH₂, or NHAc;

R³ independently represents H, CO₂R⁵ or CH₂CO₂R⁵;

R⁴ independently represents H, OH, O-(C₁-C₈)alkyl, OM^{e+}, or a group selected from the group consisting of:

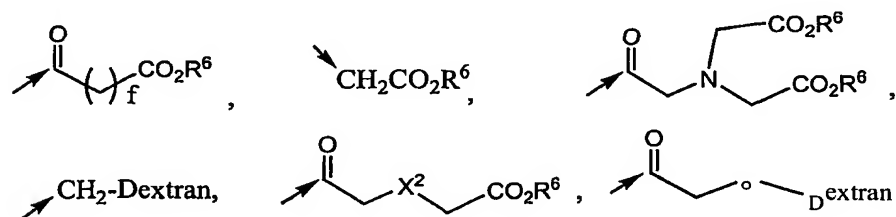




M independently represents Na, K or a pharmaceutically acceptable metal ion;

e = 1-3;

R^5 independently represents at each occurrence H, M^{e+} , (Ci-Cs)alkyl, $(C_3\text{--}C_8)$ cycloalkyl, substituted $(C_5\text{--}C_{14})$ aryl, hetero $(C_2\text{--}C_{14})$ aryl, $C(=O)(CH_2)_fCHR^9CO_2R^5$, $CH_2C(=O)OR^5$, $P(=O)(OR^5)_2$,



X^2 independently represents O, S, SO, SO₂, or NR⁵;

R⁶ independently represents H, Na⁺, K⁺ any other pharmaceutically acceptable metal ion, (C₁-C₈)alkyl, or (C₃-C₈)cycloalkyl;

R⁷ independently represents at each occurrence same or different R⁵;

R⁸ independently represents CH₂, O, NR⁴, S, S=O or O=S=O;

R⁹ independently represents H, (Ci-C₈)alkyl or an amino acid;

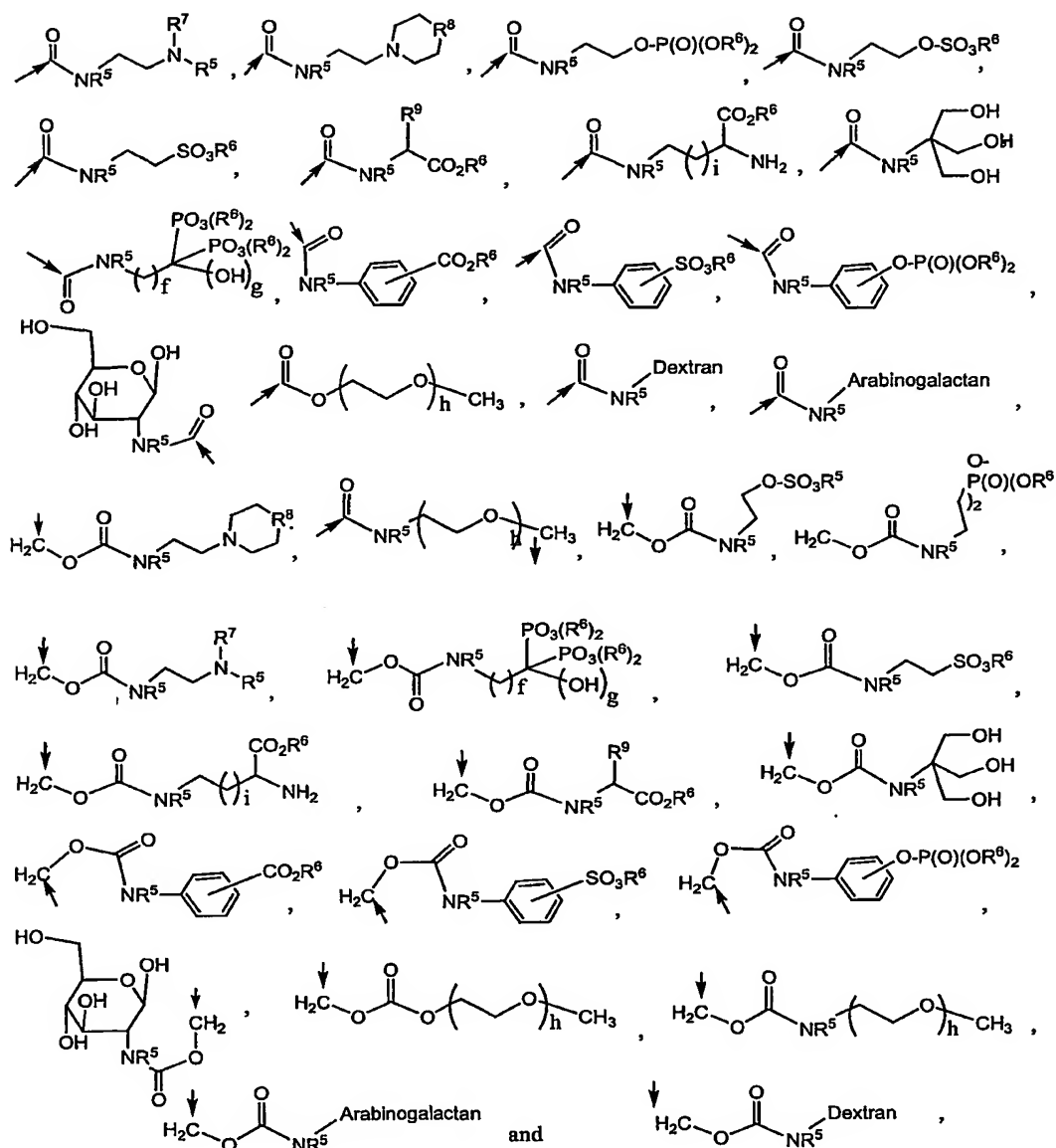
f is 0-6;

g is 0-1;

h is 1-2000;

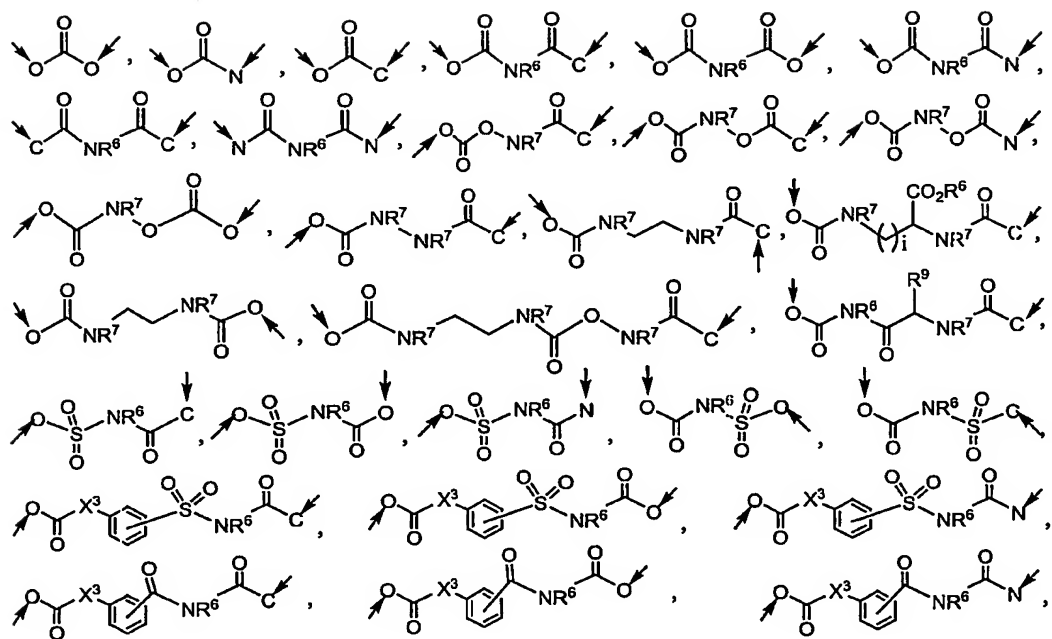
i is 1-4;

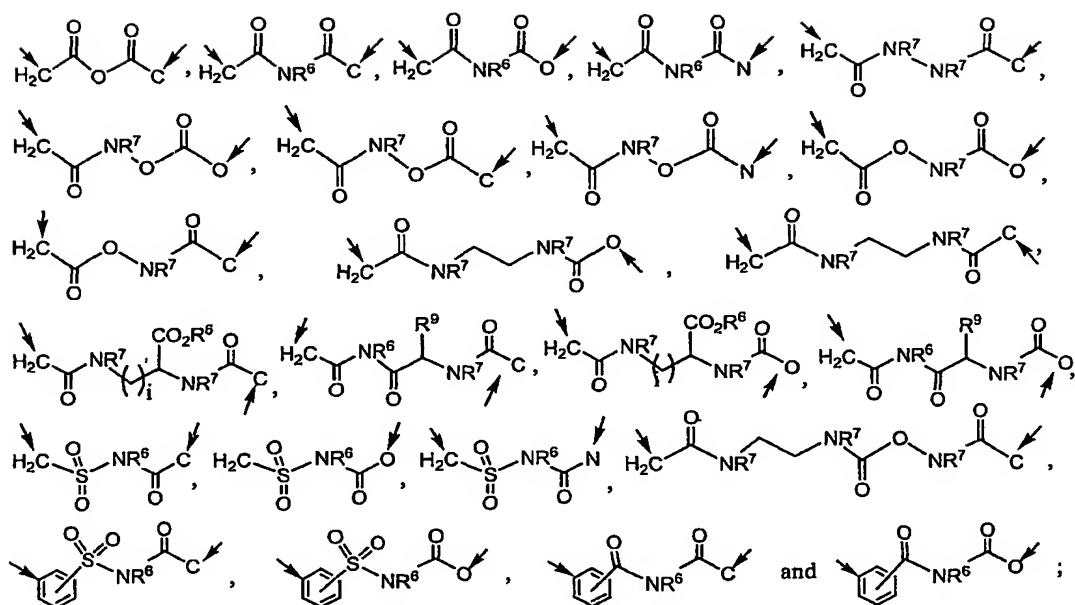
R¹⁰ and R¹¹ independently represent H, (Ci-C₈)alkyl, (C₃-C₈)cycloalkyl, or a group selected from the group consisting of:



with a proviso that when R¹⁰ is selected from the above group, R¹¹ represents H or (C₁-C₃)alkyl, and when R¹¹ is selected from the above group, R¹⁰ represents H or (C₁-C₃)alkyl;

R^{12} independently represents a group selected from the group consisting of:



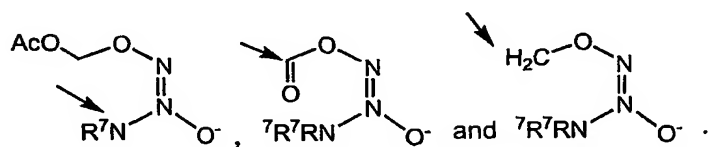


X³ is independently 0 or NR⁷.

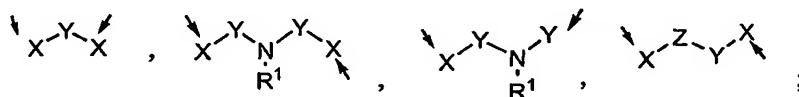
2. The compound according to claim 1, wherein a is 0.

3. The compound according to claim 2, wherein D^2 is a group or molecule comprising one or more water solubilizing functional groups selected from the group consisting of hydroxyl, amino, acylamino, carboxyl, sulphate, sulfonate, phosphate, phosphonate, N-acysulfonamide, N-acysulfamate, N-acylcarbamate, N-acylcarbamate metallic salts, and amino acids to form water-soluble prodrugs.
4. The compound according to claim 2, wherein D^2 is selected from the group of amino acids consisting of Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.
5. The compound according to claim 2 wherein D^2 is a polymer.
6. The compound according to claim 5, wherein the polymer is selected from the group consisting of dextran, modified dextran, arabinogalactan, polyamino acids, and polyethylene glycol.
7. The compound according to claim 6, wherein the polymer is a polyaminoacid selected from group consisting of poly(l-glutamic acid), poly(d-glutamic acid), poly(dl-glutamic acid), poly(l-aspartic acid), poly(d-aspartic acid), poly(dl-aspartic acid), copolymers of the polyaminoacids and polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyacrylic acid, poly(2-hydroxyethyl 1-glutamine), dextran aldehyde, carboxymethyl dextran, arabinogalactane aldehyde, carboxymethyl arabinogalactane, and hyaluronic acid.
8. The compound according to Claim 5, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltons.
9. The compound according to Claim 5, wherein the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.
10. The compound according to claim 2 wherein D^2 is a dipeptide.
11. The compound according to claim 2, wherein D^2 is a vitamin selected from the group consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5.

12. The compound according to claim 2, L^2 is O; A and A^1 are independently $(CH_2)_d$, 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; d is 1-4; B is S-S, S-S=O, S-SO₂ or S-S=NH; D^2 is NO, NO₂ or a NONOate selected from the group consisting of:



13. The compound according to claim 2, wherein L^2 is O; A and A^1 are CH_2 ; E is CH_2 ; B is a bond or $(CH_2)_b$; b is 1-6; a is O; D^2 is NO₂ and L^1 is a group selected from

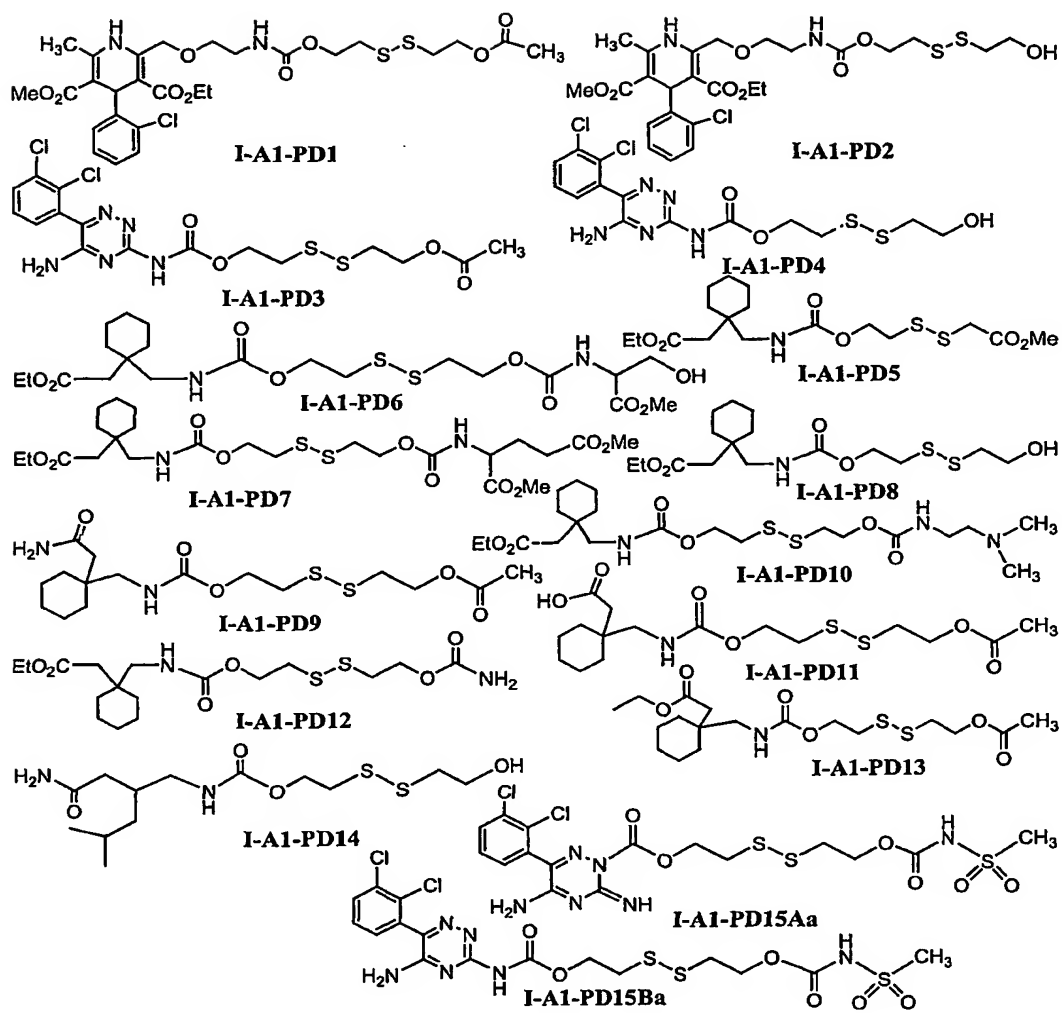


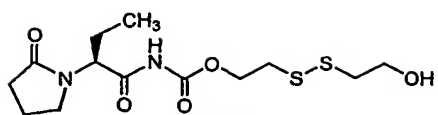
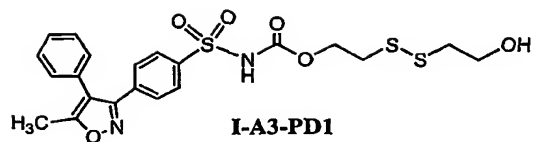
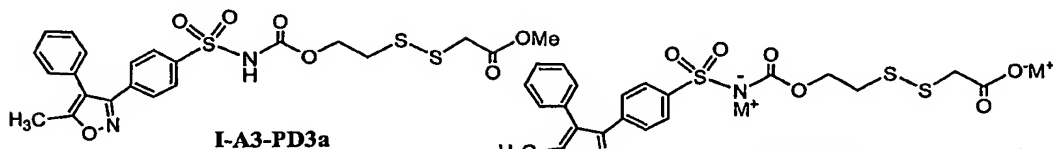
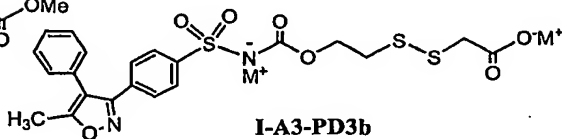
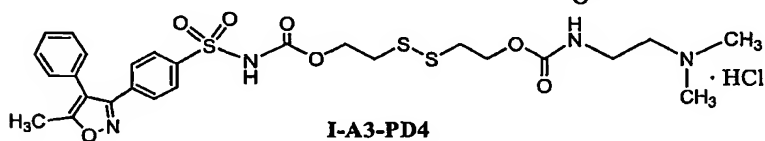
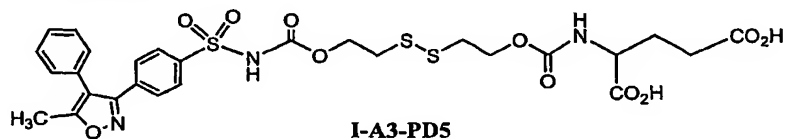
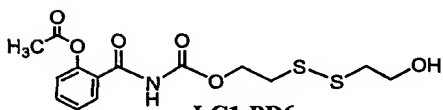
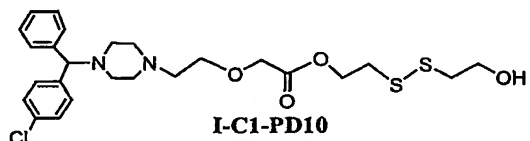
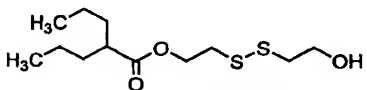
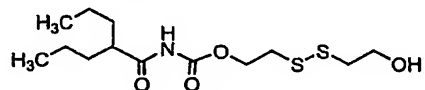
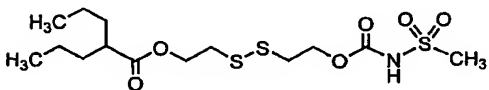
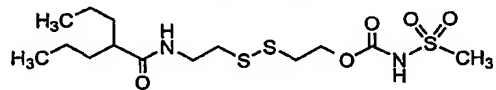
wherein,

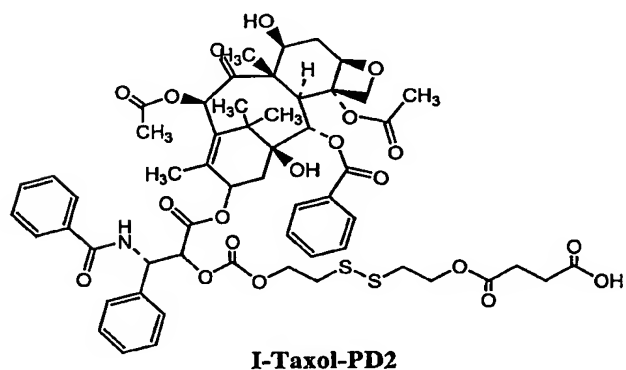
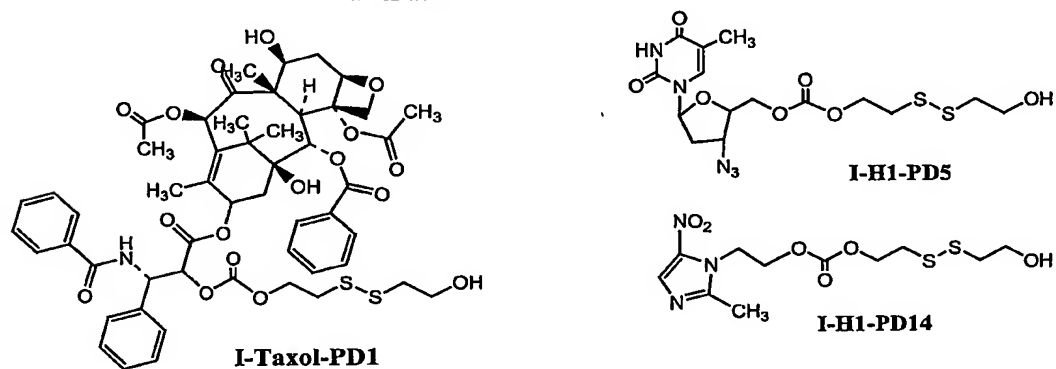
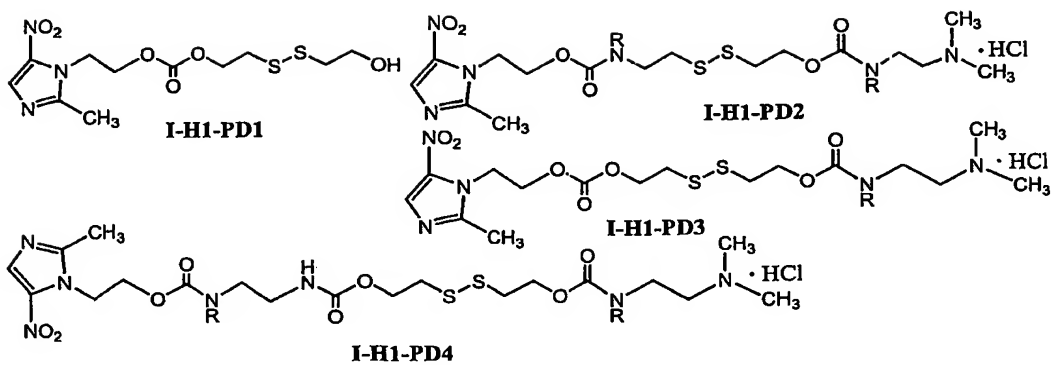
X is O, S or NR^1 ; and

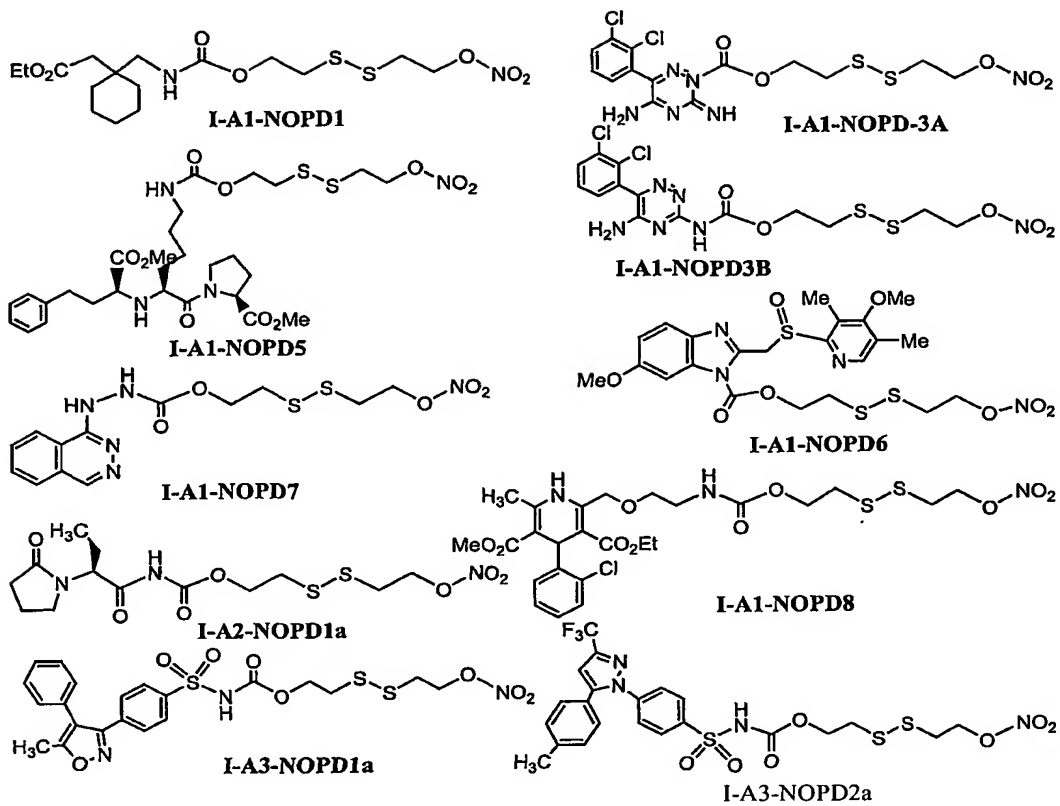
Y and Z are as defined.

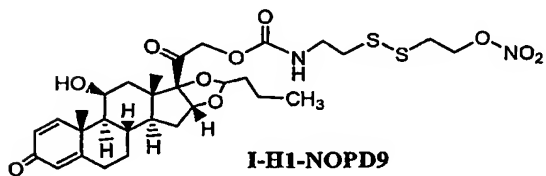
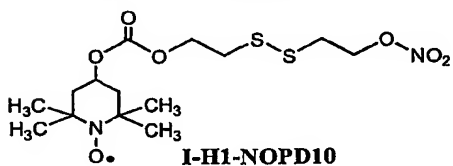
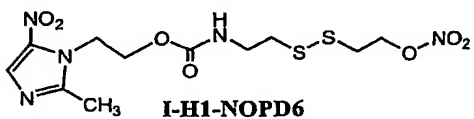
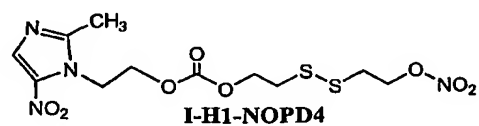
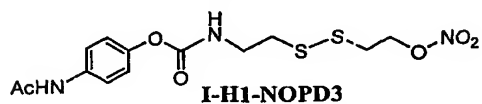
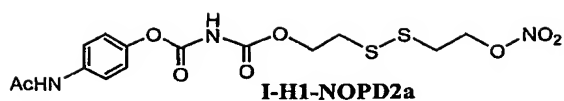
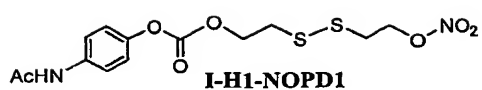
14. The compound according to claim 2, selected from the group consisting of:

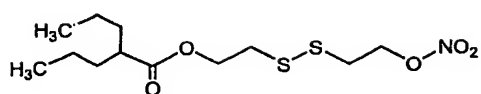
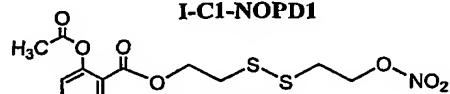
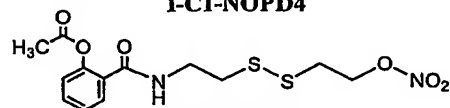
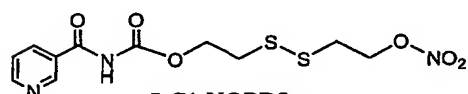
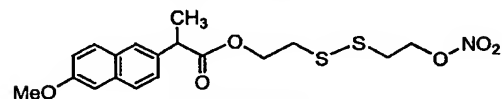
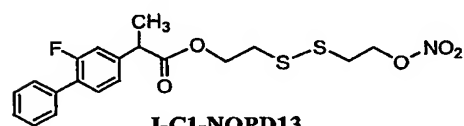
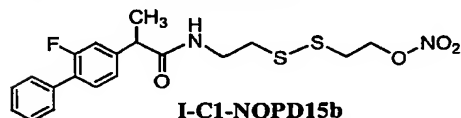
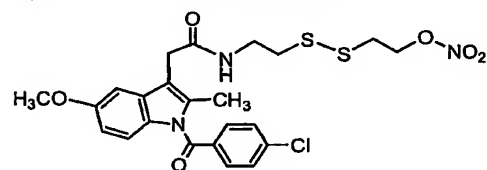
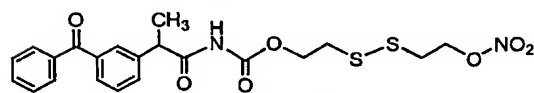
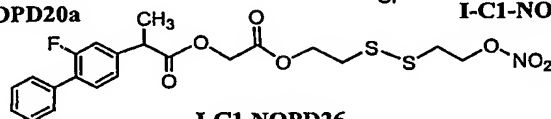
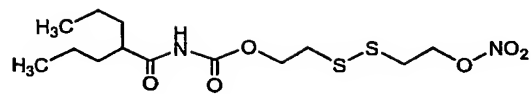
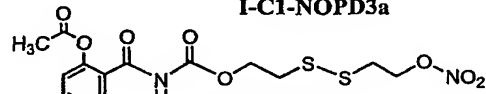
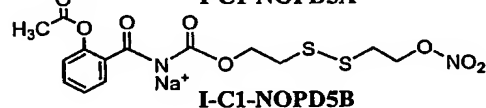
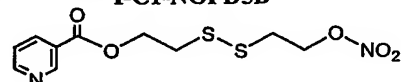
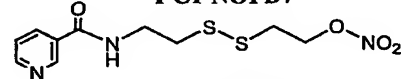
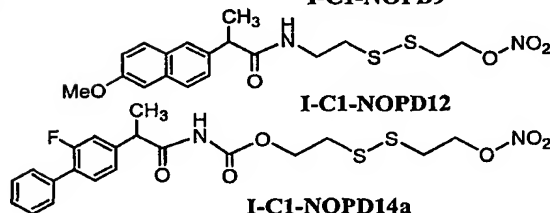
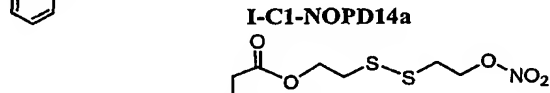
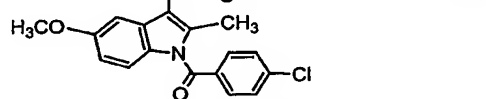
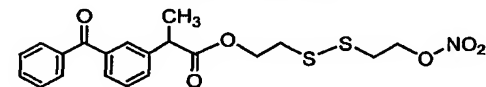
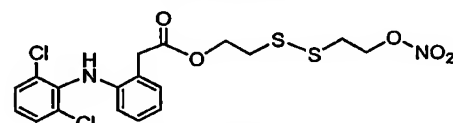


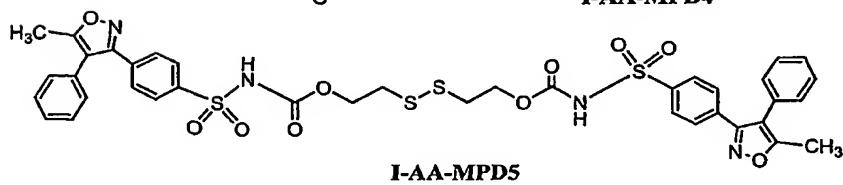
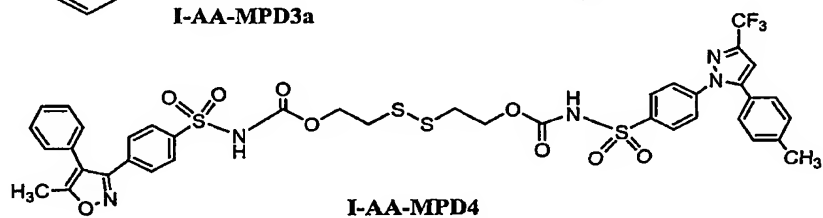
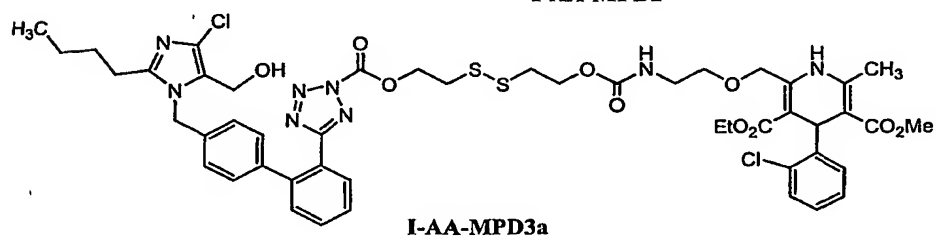
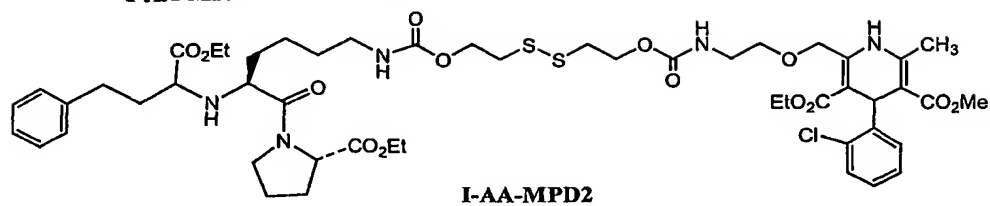
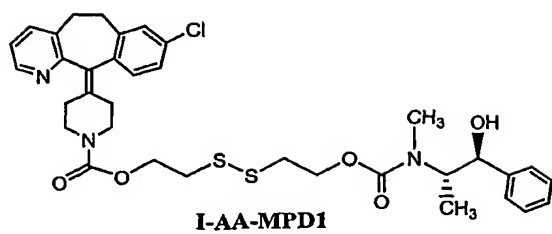
**I-A2-PD1****I-A3-PD1****I-A3-PD3a****I-A3-PD3b****I-A3-PD4****I-A3-PD5****I-C1-PD6****I-C1-PD10****I-C1-PD11****I-C1-PD13****I-C1-PD14****I-C1-PD15a**

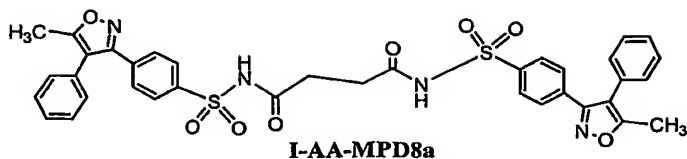
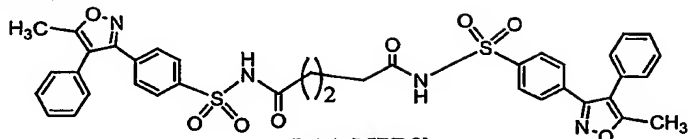
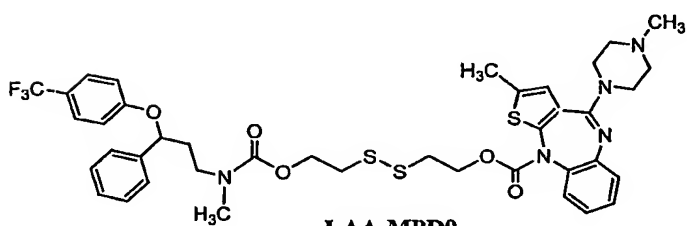
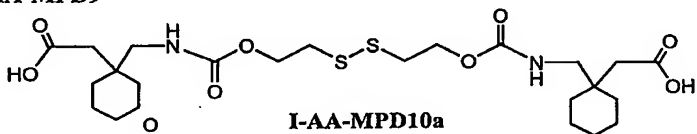
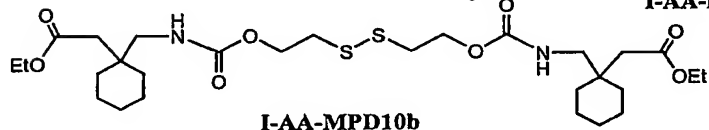
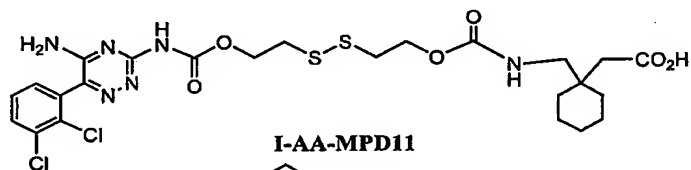
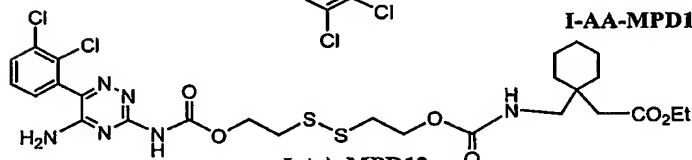
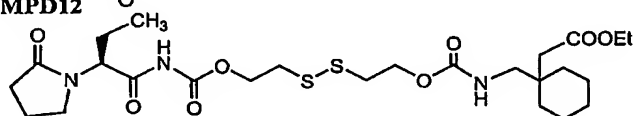


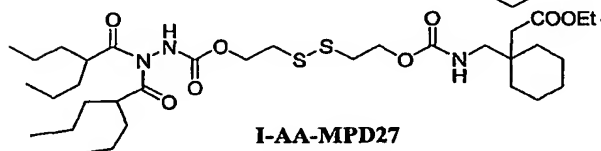
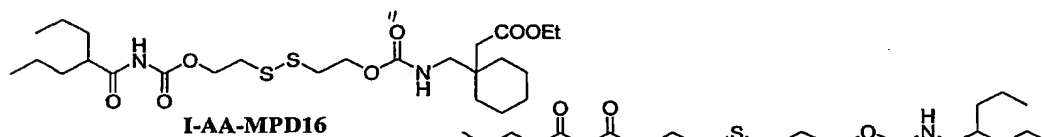
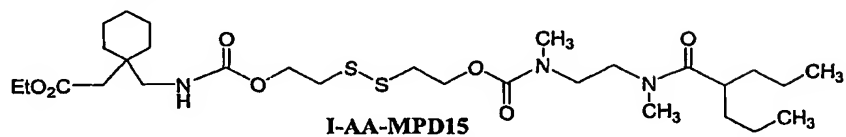
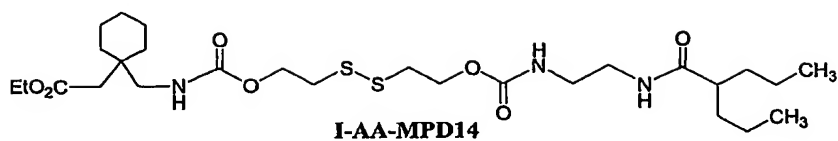
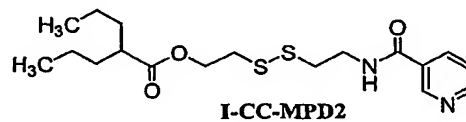
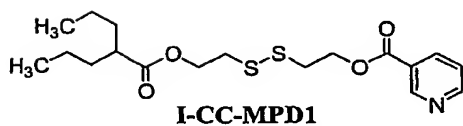
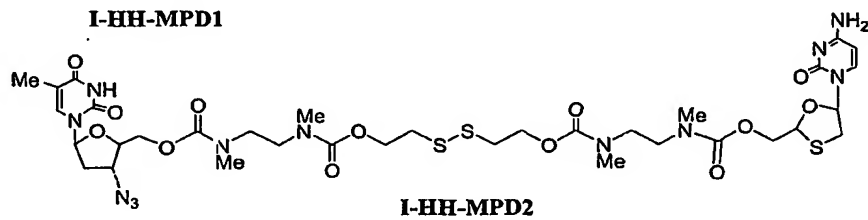


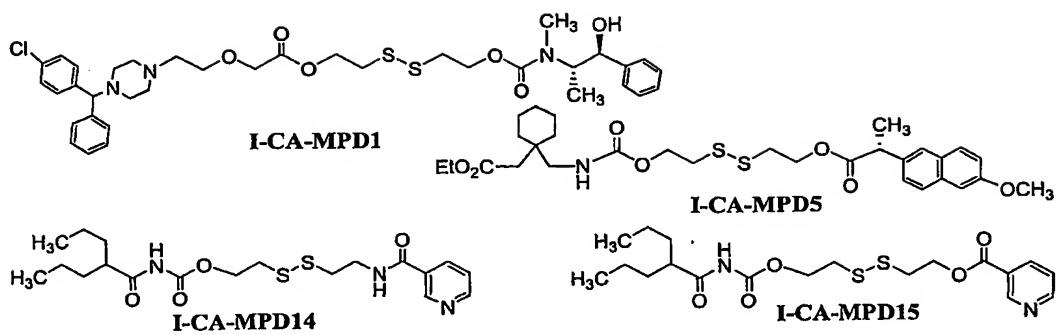


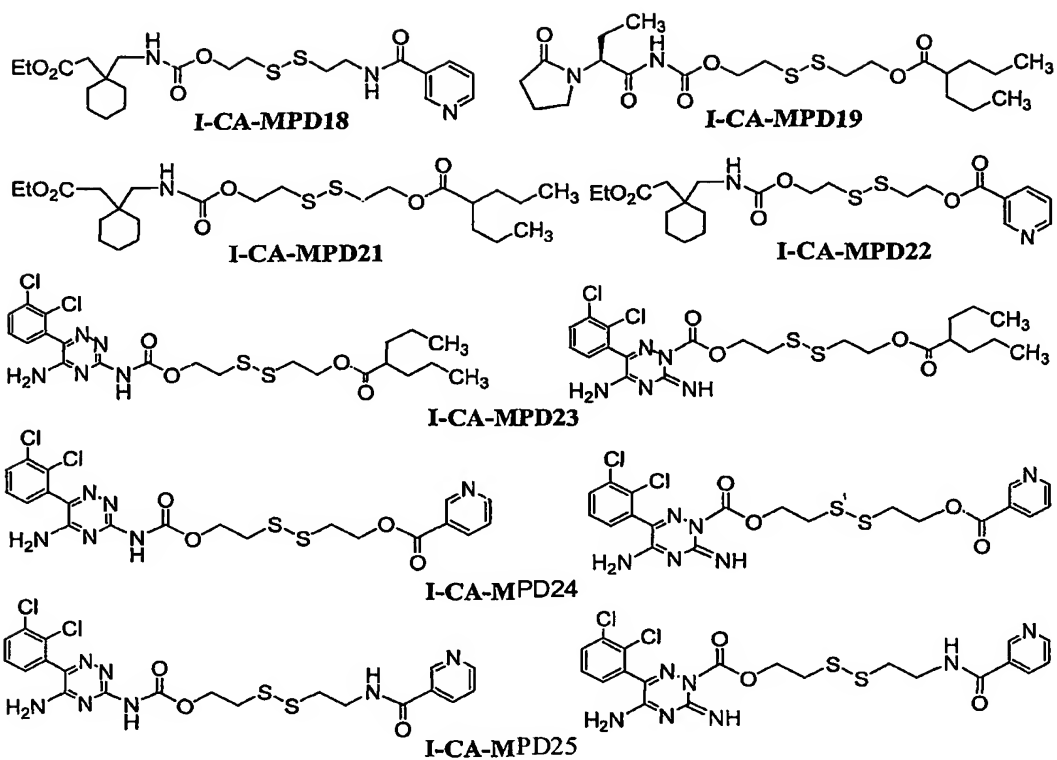
**I-C1-NOPD1****I-C1-NOPD4****I-C1-NOPD6****I-C1-NOPD8a****I-C1-NOPD10****I-C1-NOPD13****I-C1-NOPD15b****I-C1-NOPD18****I-C1-NOPD20a****I-C1-NOPD26****I-C1-NOPD3a****I-C1-NOPD5A****I-C1-NOPD5B****I-C1-NOPD7****I-C1-NOPD9****I-C1-NOPD12****I-C1-NOPD14a****I-C1-NOPD16****I-C1-NOPD19****I-C1-NOPD22**

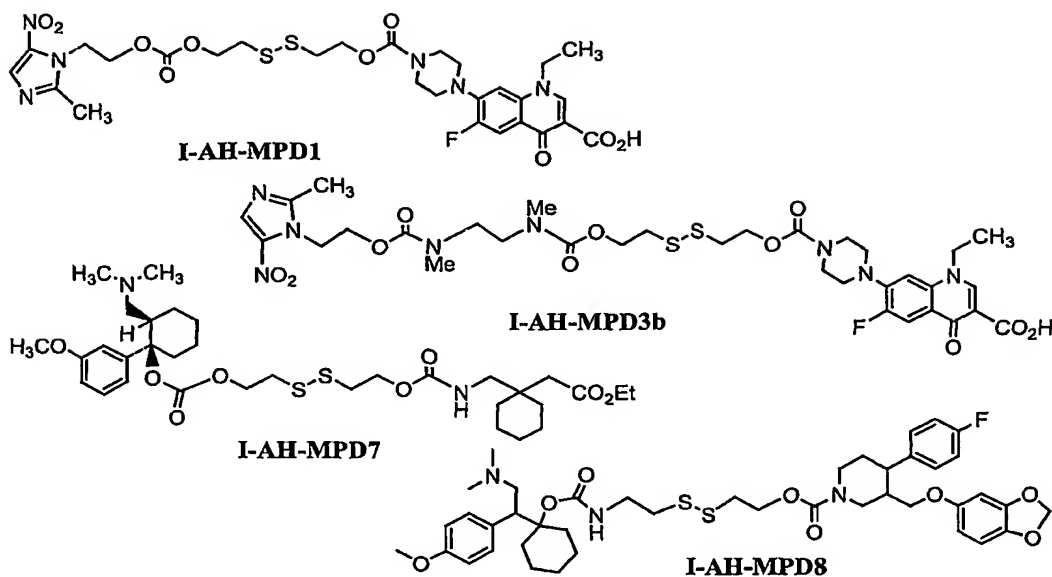


**I-AA-MPD8a****I-AA-MPD8b****I-AA-MPD9****I-AA-MPD10a****I-AA-MPD10b****I-AA-MPD11****I-AA-MPD12****I-AA-MPD13**

**I-AA-MPD22**







15. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 2, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.
16. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 14, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.
17. The compound as in claim 2, wherein D¹ and D² represent known and investigational amino-, hydroxyl-, carboxyl-, and keto- containing drugs compiled in drug databases comprising the Merck Index, IDdb, Prous Science's Integrity®, Prous Science Drugs of the Future™, and The Ensemble®.
18. The composition of claim 15 comprising therapeutically effective amount of pairs of drugs selected from: Paclitaxel and Doxorubicin; Paclitaxel and Mitomycin C; Paclitaxel and 9-aminocamptothecin; 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP), 3-Aminopyridine-4-methyl-2-carboxaldehyde thiosemicarbazone (3-AMP) and Paclitaxel, Doxorubicin, Mitomycin C; CC-1065 and Paclitaxel, Doxorubicin, Mitomycin C; Trans-Resveratrol [(E)-3,4',5-trihydroxystilbene]

and Paclitaxel, Doxorubicin, Mitomycin C; Retinoic acid and Butyric acid; Paclitaxel and Captopril; Doxorubicin and Biotin; 5-Fluorouracil and Cytarabine; Edatrexate and Paclitaxel; Cephalosporanic acid and Paclitaxel; Cephalosporin and Paclitaxel; Paclitaxel and Gemcitabine; Levodopa and Carbidopa; Amoxicillin and Clavulanic acid; Ampicillin and Clavulanic acid; Amoxicillin and Pencillinic acid sulfone; Ampicillin and Pencillinic acid sulfone; Olivanic acid and 3-substituted Z-2-acylaminopropionic acid; Lofibrol and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Ezetimibe and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Amlodipine and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Metformin and Nateglinide/Glipizide/Glibenclamide (Glyburide); Metformin and Lovastatin/Pravastatin/Fluvastatin/Atorvastatin/Simvastatin; Pseudoephedrine and Fexofenadine/Cetirizine/Desloratadine/Epinastine; Salbutamol and Ipratropium bromide; Mometasone and Formoterol/Salmeterol; Fluticasone and Formoterol/Salmeterol; Budesonide and Formoterol/Salmeterol; Declofenac and Misoprostol; Declofenac and Omeprazole/Lansoprazole/Rabeprazole/Lemnoprazole/Pantoprazole; Naproxen and Propfenazone; Acetaminophen and chlorzoxazone/metaxalone/mephenoxalone; Zidovudine and Lamivudine; Triple prodrug of Zidovudine; Lamivudine and Abacavir (Ziagen); Lopinavir and Ritonavir; Lamivudine and Adefovir/dipivoxil; Amprenavir and Zidovudine; Nelfinavir and Zidovudine/Lamivudine; Stavudine and Zidovudine/Lamivudine; Dideoxyinosine and Zidovudine/Lamivudine; Emtricitabine and Penciclovir/Famciclovir; Acyclovir and deoxycholate/chenodeoxycholate and ursodeoxycholate; Triple and Zidovudine; and Lamivudine and Efavirenz;

19. A therapeutically effective amount of the pharmaceutical composition as in claim 15, comprising a two or more drugs, a drug and its own prodrug, a drug and a different prodrug, two different prodrugs, a drug and a mutual prodrug, mutual prodrug and its own drugs or a mutual prodrug and one of its constituent drugs.

20. The compound according to claim 2, wherein D¹ and D² are therapeutic agents selected from the group consisting of: Sedatives, Hypnotics, Antidepressants, Antipsychotics and Antimanics, Analgesics, Antipyretics, Antimigraine agents, Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for dementia, Antiemetics, drugs for Vertigo, CNS Stimulants activators; Antiinfective eye

preparations; Antiinflammatory; antiallergic preparations, antiglucoma drugs; preparations to cure eye diseases; aural, nasal and oropharyngeal preparation, Antiarrhythmic drugs, Antihypertensives, alfa/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor antagonists, diuretics, Antianginals, nitrates, calcium channel blockers, Drugs for cardiac failure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics, antiplatelet drugs, Respiratory stimulants, Antitissives, Expectorants, Mucolytics, Decongestants, Antihistamine agents, antiasthmatics; Antiulcer, Antisecretory drugs, H₂ receptor antagonists, Proton Pump Inhibitors, Prostaglandin analogues, Antacids, Antispasmodics, drugs modifying intestinal motility, Antidiarrhoeals, antimotility drugs, antimicrobial drugs, drugs acting on gall bladder, Urinary antiinfectives, Diuretics, Urinary analgesics, Antispasmodics, Antiinfective drugs acting on urethra and vagina, drugs acting on uterus, Drugs for prostatic hypertrophy, alfa blockers, antiandrogens, Drugs for erectile dysfunction, Spermicidal, nonhormonal contraceptives, Emollients, keratolytics, topical antiinfectives, topical antifungals, topical parasiticidal, topical steroids, topical drugs for acne vulgaris, drugs for psoriasis, pigmentation disorders, and Antiseborrhoeics, Non Steroidal Anti Inflammatory Drugs (NSAIDs), COX-2 inhibitors, Antiarthritic agents, Immunosuppressants, Topical analgesics, Muscle relaxants, Neuromuscular Drugs, Penicillin antibiotics, Cephalosporin antibiotics, Quinolone, Fluoroquinolone antibiotics, Macrolide antibiotics, Chloramphenicol, Tetracycline antibiotics, Sulfonamides, Antianaerobics, Metronidazole, Antitubercular drugs, Antileprosy drugs, Antifungals, Antiprotozoals, Anthelmintics, Antiinfective Drugs, Antimalarials, Antivirals, Anabolics, androgenic steroids, Corticosteroids, Oestrogens, Progestogens and Hormonal contraceptives, Fertility Agents, Tropic hormones and related drugs, Thyroid and antithyroid drugs, Antidiabetics and hyperglycaemics, Vitamins, Amino acids, Anti-obesity drugs, Hypolipidaemic drugs, fibric acid derivatives, statins, HMG CoA reductase inhibitors, nicotinic acid group, drugs used for Gout, drugs affecting bone metabolism, bisphosphonates, Anticancer drugs, alkylating agents, cytotoxic antibiotics, antimetabolites, cytarbine, Fludarbine, 5-Fluorouracil, Mercaptopurine, Thioguanine, Vinca alkaloids, Etoposide, Taxanes, Topoisomerase 1 inhibitors, Cytotoxic immunosuppressants, Immunostimulants, Cytoprotectives, Amifostine, Oestrogens,

Progestogens, hormon antagonists, antineoplastic drugs, Antiallurgics, non-sedative antihistamins, Cetirizine, Desloratadine, Terfenadine, Fexofenadine, sedative histamines, histamine receptor blockers, Local anaesthetics, intravenous anaesthetics, inhalation anaesthetics, and muscle relaxants.

21. The compound according to claim 2, wherein D¹ and D² are from same or different therapeutic class and exhibit either the same or different mechanisms of action or work on same or different biological targets or work on same or different disease conditions.

22. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the composition according to claim 15.

23. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the composition according to claim 16.

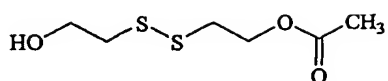
24. A method of use of the compound according to claim 2, for prevention or treatment of diseases where a chronic, sustained and selective release of the constituent drug or nitric oxide is beneficial.

25. A method of use of the compound according to claim 2, in a subject in need thereof for prevention or treatment of diseases of Central Nervous System, Eye, Ear, Nose and Oropharynx, Cardiovascular System, Respiratory System, Gastrointestinal tract system, Genito-urinary system, skin, musculo-skeletal system, Endocrine system, metabolism and neoplastic disorders, infectious diseases, allergy and immunology, and for anaesthetic, analgesic and surgical needs.

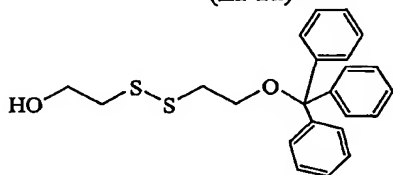
26. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of two or more compositions according to claim 15, wherein compositions used in combination to treat a patient in need of a combination therapy.

27. A method of use of composition as claimed in claim 15, for prevention and/or treatment of diseases where a chronic, sustained and selective release of the constituent drug(s) and/or nitric oxide is beneficial.

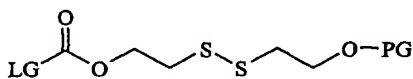
28. The novel intermediates obtained in the preparation of compounds of claim 1, wherein the intermediates are selected from:



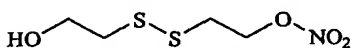
2-((2-Hydroxyethyl)disulfanyl)ethyl acetate
(LI-1a)



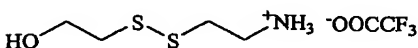
2-((2-(Trityloxy)ethyl)disulfanyl)ethanol
(LI-1c)



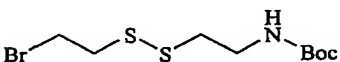
(LI-1xy)



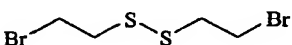
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2b)



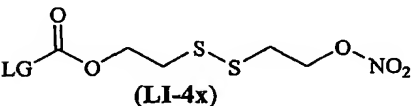
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2c.TFA)



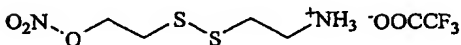
tert-Butyl 2-((2-bromoethyl)-
disulfanyl)ethylcarbamate (LI-2e)



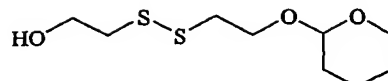
1,2-Bis(2-bromoethyl)disulfane (LI-3a)



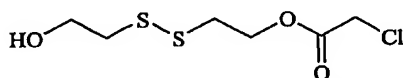
(LI-4x)



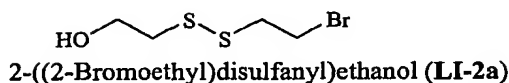
2-((2-Aminoethyl)disulfanyl)ethyl
nitrate.acid salt (LI-5.TFA)



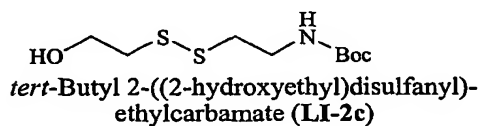
2-((2-(Tetrahydro-2*H*-pyran-2-
yloxy)ethyl)disulfanyl)ethanol (LI-1b)



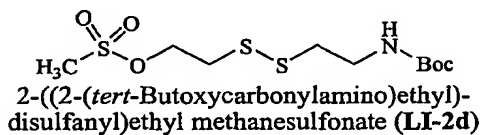
2-((2-Hydroxyethyl)disulfanyl)ethyl
2-chloroacetate (LI-1d)



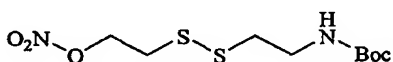
2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)



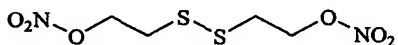
tert-Butyl 2-((2-hydroxyethyl)disulfanyl)-
ethylcarbamate (LI-2c)



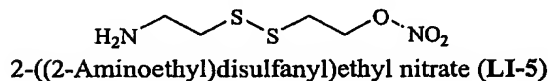
2-((2-(*tert*-Butoxycarbonylamino)ethyl)-
disulfanyl)ethyl methanesulfonate (LI-2d)



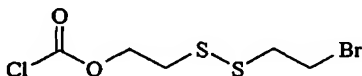
tert-Butyl 2-((2-(nitrooxy)ethyl)-
disulfanyl)ethylcarbamate (LI-2f)



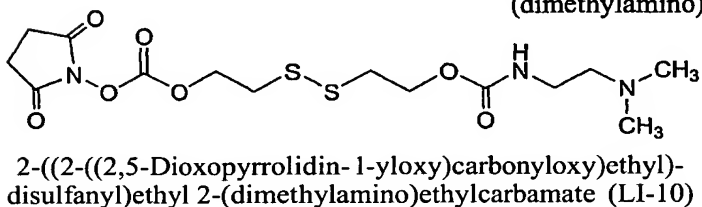
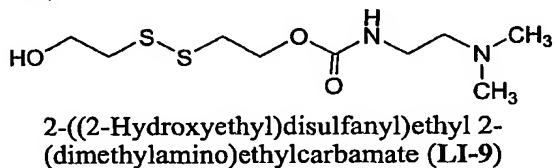
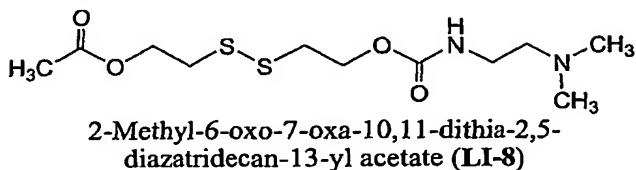
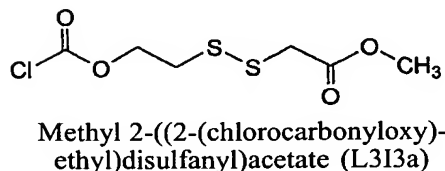
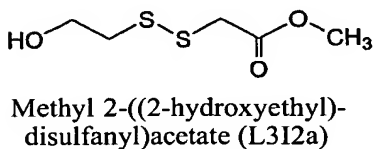
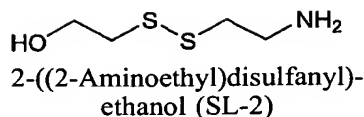
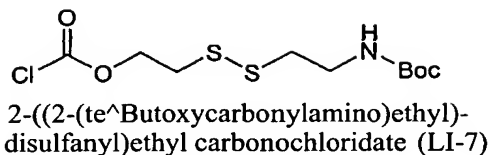
2,2'-Disulfanediyldis(ethane-2,1-diyl)
dinitrate (LI-3b)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)



2-((2-Bromoethyl)disulfanyl)ethyl
carbonochloridate (LI-6)



29. The use of the novel intermediates of claim 26, in the preparation of compounds of formula I or pharmaceutically acceptable salts thereof.

30. The process for the preparation of the compound as in claim 1, or a pharmaceutically acceptable salts thereof, wherein the process is selected from:

Process 1: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LI-Ix,

B) Converting LI-Ix, obtained in step A to an activated formyl intermediate LI-Ixy by treating with phosgene or its equivalent, and

C) Reacting LI-lxy obtained in the step B with an appropriate amino- or hydroxyl containing drug (D^1) to give the corresponding compound of formula I;

Process 2: A) Converting carboxyl containing drug (D^1) into its activated acyl halide or imidazolide or isocyanate by known methods, and

B) Reacting the intermediate obtained in the step A with the linker intermediate LI-Ix to obtain the compound of formula I;

Process 3: Mixing a selectively protected and activated drug with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) in a suitable solvent in presence of a suitable coupling agent to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D^2 is NO_2 ;

Process 4: Converting 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) into its formyl halide or imidazolide (LI-4x) by using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable amino- or hydroxy-containing drug in suitable solvent in presence of a suitable base to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D^2 is NO_2 ;

Process 5: Mixing/reacting a an appropriately protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D^2 is NO_2 ; and

Process 6: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LI-Ix,

B) Reacting formyl linker intermediate LI-lxy with amino or hydroxyl containing drug (D^1) to obtain the prodrug of formula I with free hydroxyl group on the linker,

C) Converting the intermediate obtained in the step B into activated formyl halide or imidazolide derivative, and

D) Reacting the intermediate obtained in the step C with the drug D^2 to obtain the mutual prodrug of formula I.

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

VEPACHE)DU PROFESSIONAL CORPORATION
 Atta. vepach.edu, sreenivasara
 3.230 Georgetown Way
 Vernon H.Ule, IL 60061
 UNITED STATES OF AMERICA

NOTIFICATION OF DECISION CONCERNING
 REQUEST FOR RECTIFICATION

(PCT Rule 91.1 (f))

Date of mailing (day/month/year) 16/02/2006	
Applicant's or agent's file reference NP-2005-001	RI=PLY DUE NONE However, see last paragraph below
International application N°, PCT/ I S2005/ 052797	International filing data (day/month/year) 26/08/2005
Applicant SATYAM, Appara O.	

The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the International application/in other papers submitted by the applicant to this Authority, and that it has decided:


1. ☐ to authorise the rectification;
☐ as requestor] by the applicant,
☐ to the extent set forth below*;

2. ☒ JF_ to refuse to authorize the rectification or part of it for the following reasons*:

Request received too late by ISA/EP. See RuIa 91. Kg) (i) PCT.

A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

* **If the authorization of the rectification has been refused in Whole or in part**, the applicant may request the International Bureau, before the technical preparations for international publication have been completed and subject to the payment of a fee, to publish the request for rectification together with the international application. See Rule 91.1(f), third and fourth sentences, and, for the amount of the fee, see the PCT Applicant's Guide, Volume I/A, Annex BS(IB).

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sylvia Hermier
--	--------------------------------------

IN THE EUROPEAN PATENT OFFICE

Applicant: Apparao Satyarø *et al*) Atty. Docket No.: NP-2005-001
 International Application No. :) RE: Rule 91 Rectification
 5 PCT/IB2005/052797) Date: January 25, 2006
 International Filing Date: August 26, 2005)
)
 Title: PRODRUGS CONTAINING)
 10 NOVEL BIO-CLEAVABLE LINKERS)

International Searching Authority
 Patentlaan 2
 15 2288 Eindhoven
 The Netherlands
 Fax: 0031703403016

20 REQUEST FOR RECTIFICATION UNDER RULE 91

Dear Sir;

In the above referenced patent application, applicants submit the following supplementary rectification under rule 91 for entry prior to publication.

25 1) Rectifications to PCT-SAE Electronic Filing Errors.

Rectifications to the Specification begin on page 1 of this paper.

Rectifications to the Claims begin on page 4 of this paper.

2) Rectifications to Typographical and Obvious Errors

Rectifications to the Specification begin on page 5 of this paper,

30 Rectifications to the Claims begin on page 14 of this paper.

Remarks begin on page 15 of this paper.

Substituted Specification and Claims follow page 20 of this paper, with page numbers starting from 1,

35

I) Rectifications to PCT-SAFE Electronic Filing Errors:

During PCT-SAFE filing, blank spaces were introduced between schemes and between schemes and the text. The following rectifications to delete the inadvertently introduced spaces are respectfully requested,

5

In the Specification:

Please delete the blank spaces on the following pages and rearrange the matter:

Pages 6-10

10 On page 6, please delete blank space from line 24 to the end of the page.

On page 7, please delete blank spaces at the beginning and at the end of the page.

On page 8, please delete blank space at the end of the page.

On page 9, please delete blank space at the beginning of the page.

On page 10, please delete blank space at the end of the page.

15 On page 12, please delete blank space at the beginning of the page.

On page 13, please delete blank space at the beginning of the page.

The corresponding pages in the substitute specification provided herewith are pages 6-10.

Pages 23-30

20 On page 23, please delete blank space from line 25 to the end of the page.

On page 24, please delete blank space at the beginning of the page.

On page 25, please delete blank space at the end of the page.

On page 26, please delete blank space at the beginning of the page.

On page 27, please delete blank space from line 12 to the end of the page.

25 On page 29, please delete blank space at the beginning of the page.

On page 30, please delete blank space at the beginning of the page.

The corresponding pages in the substitute specification provided herewith are pages 21-24.

Page 33

30 On page 33, please delete blank space between line 17 and the structures.

The corresponding page in the substitute specification provided herewith is page 27-

Page 36

On page 36, please delete blank space between line 6 and the structures.

The corresponding pages in the substitute specification provided herewith are pages 29-30.

5

Pages 37-46

On page 37, please delete blank space from line 12 to the end of the page.

On page 38, please delete blank space at the end of the page.

On page 40, please delete blank space at the end of the page,

10 On page 41, please delete blank spaces at the beginning and at the end of the page.

On page 42, please delete blank spaces at the beginning and at the end of the page.

On page 43, please delete blank space at the end of the page,

On page 44, please delete blank space at the beginning of the page,

On page 46, please delete blank space after first two lines to the end of the page.

15 The corresponding pages in the substitute specification provided herewith are pages 31-37.

Pages 50-51

On page 50, please delete blank spaces at the beginning and at the end of the page.

On page 51, please delete blank space at the end of the page.

20 The corresponding pages in the substitute specification provided herewith are pages 40-41.

Page 56

On page 56, please move the sentence at the end of the page to top of next page.

The corresponding page in the substitute specification provided herewith is page 45.

25

Page 59

On page 59, please move the sentence at the end of the page to the top of next page.

The corresponding page in the substitute specification provided herewith is page 49.

30 Page 71

On page 71, please move the sentence on the page to the top of next page.

The corresponding page in the substitute specification provided herewith is page 60.

Page 89-91

On page 89, please delete blank space at the end of page.

- 5 On page 90, please delete blank spaces at the beginning and at the end of the page.

On page 91, please delete blank spaces at the end of the page.

The corresponding pages in the substitute specification provided herewith are pages 77-79.

Page 94

- 10 On page 94, please delete blank space at the end of the page.

The corresponding page in the substitute specification provided herewith is page 81.

Page 97-98

On page 97, please delete blank space between the structures.

- 15 On page 98, please delete blank space at the beginning of the page;

The corresponding pages in the substitute specification provided herewith are pages 84-85,

Page 103

On page 103, please delete blank space from line 6 to the end of the page.

- 20 The corresponding page in the substitute specification provided herewith is page 90.

Pages 132 -133

On page 132, please delete blank space at the beginning of the page.

On page 133, please delete blank spaces at the beginning and at the end of the page.

- 25 The corresponding page in the substitute specification provided herewith is 118.

In the Claims:

Pages 203-231

On page 203, please delete blank space at the end of the page.

- 30 On page 204, please delete blank space at the beginning of the page.

On page 205, please delete blank spaces at the beginning and at the end of the page.

On page 206, please delete blank space at the beginning of the page.

On page 207, please delete blank space at the end of the page.

On page 209, please delete blank space at the beginning of the page.

On page 210, please delete blank space at the beginning of the page.

5 On page 216, please delete blank space at the end of the page.

On page 217, please delete blank spaces at the beginning and at the end of the page.

On page 222, please delete blank space at the end of the page.

On page 223, please delete blank space at the end of the page.

The corresponding pages in the substitute claims provided herewith are pages 188-210.

10

OTHER OBVIOUS ERRORS

RECTIFICATIONS TO THE SPECIFICATION

15 On page 13

At line 7: Please insert V after "one".

The corresponding page in the substitute specification provided herewith is page 10, line 7.

On page 15

20 At line 6: Please delete "and" after "secondary" and insert "and phenolic" after "tertiary",

At line 8: Please delete "or" after "secondary" and insert "or phenolic" after "tertiary".

At line 14: Please delete "cyclobutyl".

At line 17: Please insert "cyclobutyl" after "cyclopropyl".

At line 33: Please replace y with "." after "like".

25 The corresponding pages in the substitute specification provided herewith, are page 17, lines 7, 9, 15 and 16 and page 13, line 2,

On page 18

At line 6: Please insert "by" after "described".

30 The corresponding page in the substitute specification provided herewith is page 15, line 9.

On page 22

At line 2: Please replace "then" with "the".

At line 22: Please introduce a space after "entirety."

- 5 At line 29: Replace "likes" with "like".

At line 31: Replace "likes" with "like".

The corresponding page in the substitute specification provided herewith is page 19, line 3, 23 and 30, and page 20, line 2.

- 10 On page 33

At line 2: please replace "CH₂CH" with "CH₂CH₂".

The corresponding page in the substitute specification provided herewith is page 27, line 2,

On page 35

- 15 At line 1: Please replace "embodiment" with "embodiment" and "D2" with "D2".

The corresponding page in the substitute specification provided herewith is page - 110 -,

At line 9: Please replace "a" with "an".

The corresponding page in the substitute specification provided herewith is page 28, line 22.

- 20 On page 36

At line 2: Please replace "R1" with "R1".

The corresponding page in the substitute specification provided herewith is page 2, line 20.

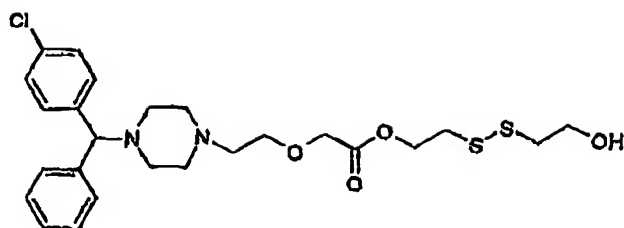
On page 37

- 25 At line 8, please replace "R1" with "R1".

The corresponding page in the substitute specification provided herewith is page 3, line 21.

On page 38

Please replace the incorrect structure of ICI-PDIO with the correct structure as shown below;



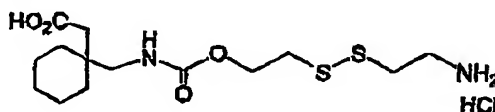
I-Cl-PDIO

If the corresponding page in the substitute specification provided herewith, is page 31.

5

On page 40

Please introduce the missing I-A1-PD18 along with its structure as shown below

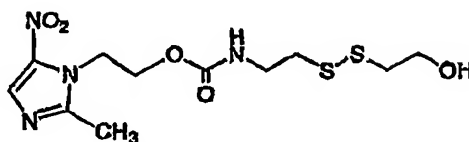


I-A1-PD18

10 The corresponding page in the substitute specification provided herewith is page 33,

On page 44

Please replace the incorrect structure of I-HWD14 with the correct structure as shown below;



15

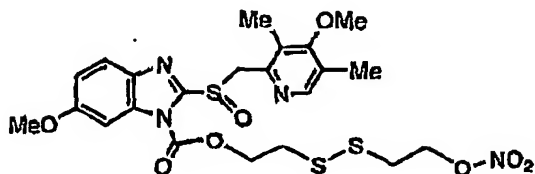
I-H1-PDX4

The corresponding page in the substitute specification provided herewith is page 35.

20

On page 49

Please replace the incorrect structure of **I-A1-NOKD6** with the correct structure as shown below;



5

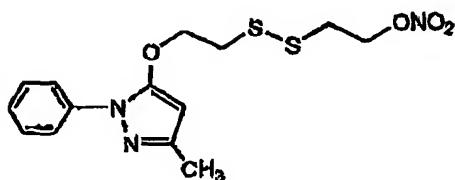
I-A1-NOPD6

The corresponding page in the substitute specification provided herewith is page 39,

On page 51

Please introduce the missing **I-H1-N0FD11** along with its structure as shown below:

10



I-H1-NOPD11

The corresponding page in the substitute specification provided herewith is page 40.

15

At line 14 below the structures please replace "Prodrugs" with "Prodrugs"

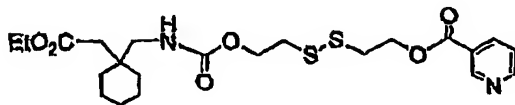
The corresponding page in the substitute specification provided herewith is page 41, Hue 1.

On page W

Please replace the incorrect structure of **I-CA-MPD22** with the correct structure as shown

20

below:



I-CA-MPD22

The corresponding page in the substitute specification provided herewith is page 50.

5 On page 73

At line 5: Please replace ";" after the word "formula" with ".".

The corresponding page in the substitute specification provided herewith is page 61, line 3.

On page 79

10 At line 16, please insert "comprises" after "invention".

The corresponding page in the substitute specification provided herewith is page 67, line 16.

On page 86

At lines 16-18, please change the text to bold font, add a space between line 15 and 16 and

15 delete the space between lines 17 and 18,

The corresponding page in the substitute specification provided herewith is page 74.

On page 98

At line 6: Please replace "form" with "from"

20 At line 11: Please replace "Schctoea" with "Scheme".

The corresponding page in the substitute specification provided herewith is page 85, lines 2 and 7.

On page 99

25 At line 1: Please insert "that" after "possible".

The corresponding page in the substitute specification provided herewith is page 85, line 17.

On page 100

In Scheme M2 please replace "Intermediate" with "Interjtnediate" before "Conjugate 'a'".

30 The corresponding page in the substitute specification provided herewith is page 89.

On page 103

At line 2: Please replace "generate" with "generate".

The corresponding page in the substitute specification provided herewith is page 92, line 2.

5

On page 106:

At line 2: Please delete "NO- releasing" and insert "of formula I" after "prodrugs".

At line 10: Please insert 'W' after "such".

At line 24: Please replace 'V' with "." after "lumexolol"

10 At line 28: Please replace ",," with "." after "Tixocortol",

The corresponding page in the substitute specification provided herewith is page 92, lines 5, 14, 27 and 31.

On page 112

15 At line 1: Please replace "keto-containing β mg" with "keto-containing*".

At line 11: Please replace '1' with '1v' after "propionic acid".

The corresponding page in the substitute specification provided herewith is page 98, line 1 and 12.

20 On page 117

At line 25: Please replace "transretinol" with "trans-retinol"

The corresponding page in the substitute specification provided herewith is page 99, line 25.

On page 117

25 At line 25: Please replace "including*" with "including".

The corresponding page in the substitute specification provided herewith is page 103, line 25.

On page 118

At Line 30: Please replace "luminostimulants" with "luminostimulants".

30 The corresponding page in the substitute specification provided herewith is page 104, line 30.

On page 119

At line 9: Please delete "NO-releasing"

At line 11: please replace "occasionally" with "occasionally"

At line 24: Please replace "," with "V" after "Gemcitabine".

- 5 The corresponding page in the substitute specification provided herewith is page 105, lines 9, 11, and 24.

On page 120

At line 17: Please replace "?" with "." after the word "like".

- 10 At line 21: Please replace "PEPATITIS B" with "HEPATITIS B".

At line 30, please delete "and" after "Triple",

The corresponding page in the substitute specification provided herewith is page 105, lines 17, 21 and 30.

- 15 On page 121

At line 1: Please delete the repeated word "the" before "present".

At line 6: Please replace "should" with "should".

At line 7: Please delete "nitrate ester (NO-releasing)" after "form of".

At line 10: Please replace "composition." with "composition" after pharmaceutical and delete

- 20 "NO" after "their".

At line 11: Please delete "releasing" before "prodrug".

At line 28: Please replace "paracetamol" with "paracetamol".

The corresponding page in the substitute specification provided herewith is page 107, lines 1, 6, 7, 10, 11 and 28.

- 25

On page 150

At line 9, please replace "RT" with "RT".

At line 13, please insert "was added" after "(5 mL".

The corresponding page in the substitute specification provided herewith is page 135, lines 9

- 30 and 10.

On page 151

At line 19, please replace "Scheme 14, Method B" with "Scheme 2".

The corresponding page in the substitute specification provided herewith is page 136, line 19,

5 On page 152

At line 2, please replace 'Intermediate 1' with "prodrug".

At line 24, please replace "Synthesis" with "Synthesis".

The corresponding page in the substitute specification provided herewith is page 137, lines 2 and 24,

10

On page 154

At line 18; Please insert "I-AMPD10" after "of".

The corresponding page in the substitute specification provided herewith is page 139, line 18,

15 On page 156

At line 28; please delete "end" after "solution of",

At line 28: Please replace "I-A1-PD16" with "I-A1-PD1S".

The corresponding page in the substitute specification provided herewith is page 141, line U and 28.

20

On page 157

At line 8: Please replace "I-A1-PD16" with "I-A1-PD1S".

The corresponding page in the substitute specification provided herewith is page 142, line 8.

25 On page 158

At line 2, please insert "in" after "dissolved" before "DCM".

The corresponding page in the substitute specification provided herewith is page 143, line 2,

On page 160

30 At line 6, please insert "the above intermediate (2.5 mL) and" after "A mixture of".

The corresponding page in the substitute specification provided herewith is page 145, line 6,

On page 169

At line 1, please insert "to the" after "according".

The corresponding page in the substitute specification provided herewith is page 154, line 1.

5 On page 173

At line 22, please insert "BOC deprotected" after "solution of

At line 22, please insert and "and then deprotected using a known general deprotectfon method" after "Method CM

10 The corresponding page in the substitute specification provided herewith is page 158, lines 22 and 23,

On page 176

At line 25, please replace "15" with "17".

15 The corresponding page in the substitute specification provided herewith is page 161, line 2S.

On page 177

At line 2, please insert ":" at the end, and on line 2, please replace "¹⁵H" with "t7".

The corresponding page in the substitute specification provided herewith is page 162, line 2,

20 On page 186

At lines 2-4, please delete the incorrect NMR data shown below;

¹H-MMR: (CDCl₃, 300 MHz): 2.21 (s, 3H), 2.36 (s, 3H), 2.93-3.05 (m, 2H), 3.19-3.28 (m, 2H), 3.88 (s, 3H), 3.92 (3, 3H), 4.70-4.87 fat, 6H), 7.10-7.50 (m, 3H), 8.10 (s, 1H).

25 The corresponding page in the substitute specification provided herewith is page 171, line 2.

On page ISS

At line 8, please replace "122" with "114",

The corresponding page in the substitute specification provided herewith is page J73, line 8.

30

RECTIFICATIONS TO THE CLAIMS

On page 203

At line 2, please introduce ", novel intermediates in preparation thereof, after "formula I",
The corresponding page in the substitute claims provided herewith is page 188, line 2.

5

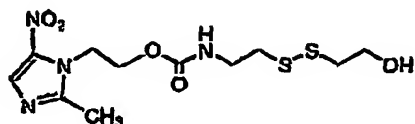
On page 207

At line 2, please insert "or" after "K⁺".

The corresponding page in the substitute claims provided herewith is page 190, line 11.

10 On page 215

Under the claim 14: Please replace the incorrect structure of **I-H1-P&14** with the correct structure as shown below:

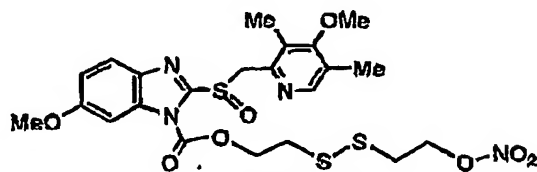


I-H1-PD14

15 The corresponding page in the substitute claims provided herewith is page 197.

On page 216

In the claim 14, please replace the incorrect structure of **I-A1-NOPD6** with the correct structure as shown below;



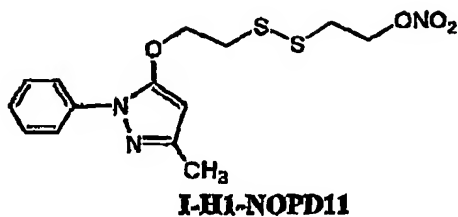
I-A1-NOPD6

20

The corresponding page in the substitute claims provided herewith is page 198,

On page 217

In the claim 14, please introduce the inadvertently omitted structure of **I-HI-NOFDIt** with the correct structure as shown below:



- 5 The corresponding page in the substitute claims provided herewith is page 198,

On page 225

At line 14, please replace "Diclofenac" with "Diclofenac" at each occurrence.

At line 22, please replace ";" with V after "Efavirenz".

- 10 The corresponding page in the substitute claims provided herewith is page 204» line 30 and page 205, line 7,

On page 230

At line 3 (in claim 29), please replace "claim 26" with "claim 28."

- 15 The corresponding page in the substitute claims provided herewith is page 209, line 3.

On page 231

At line 16, in process 5, please delete "a" before "an".

The corresponding page in the substitute claims provided herewith is page 210, line 16.

REMARKS

5 This communication addresses formatting errors during PCT-SAFE Electronic filing of the above referenced application and, under rule 91, rectification of inadvertent typographical errors, footnoting errors and omissions in the specification and claims as filed.

10 Upon recommendation of EP International Searching Authority (EP-ISA) in a telephone communication dated January 18, 2006, this communication includes and supersedes the earlier rectification request under 91 filed September 23, 2005 with WIPO Receiving Office. The rectification request filed on September 23, 2005 refers to page numbers as electronically filed. However, the Receiving Office has selectively entered the request, removed blank pages only and renumbered the pages in the application. As a result, the page numbers referred to in the previous request no longer match with the page numbers
15 in the application that is with EP-ISA. Accordingly, this request for rectification refers to only page numbers that are current in the application forwarded to EP-ISA. This communication includes a substitute specification and substitute claims, as per the EP-ISA recommendation. The corresponding page numbers in the substitute specification and claims are indicated in the rectification.

20

Rectifications to PCT-SAFE Electronic Filing Errors

The applicants request the deletion of the blank spaces and formatting errors that were inadvertently introduced in the above referenced application during the PCT-SAFE electronic filing. The errors were obvious errors caused by defective conversion and
25 transmittal of files and were not intended and shall be regarded as obvious errors in documents under PCT Rule 93.1(b). The rectification itself is obvious in the sense that anyone would immediately realize that nothing else could have been intended than what is offered as rectification. Accordingly, Applicants respectfully request the *mtry* of this correction.

30

Rectifications to Typographical and Obvious Errors

Applicant has rectified the specification and claims 1, 14 and 18. Support for the rectifications can be found throughout the specification and on, for example, page 20, lines 5-23; page 51; pages 57-59; pages 71-73; page 90; pages 106-121; page 134, scheme 14; page 149, lines 26-31; page 150, lines 1-4; page 156, lines 27-31; page 157, lines 1-10; page 161, lines 20-29; page 185, lines 25-31; page 186, lines 14; page 189, lines 11-25; and page 203. A substitute specification and substitute claims are enclosed as per EPISA recommendation. No new matter has been added by this rectification.

10 The rectifications on pages 13, 15, 18, 22, 33, 35-37, 73, 79, 86, 98-100, 103, 106, 112, 113, 117-121, 150-152, 154, 156-158, 160, 169, 173, 176, 177, 186, 188, 207, 225, 230 and 233 are formal corrections to inadvertent and obvious typographical and formatting errors. Applicants respectfully request the entry of this correction.

15 On page 15 of the specification as filed the word "phenolic" was inadvertently omitted in the description of the term "hydroxyl-containing", which has been introduced by this rectification. Support for this rectification can be found throughout the specification and particularly in structures I-H1-NOPD1, I-H1-NOPD2a, I-H1-NOPD2b, and I-H1-NOPD3 on page 51; X-HH-MPDS on page 57; I-HH-MPP13 and I-HH-MPD15 on page 58; I-HH-MPM6 and I-HH-MPD17 on page 59; I-CH-MPD4 on page 63; and illustrative examples of NO-releasing prodrugs of Paracetamol on page 89 and Mesalamine on page 90 and of Vitamin E (alpha-tocopherol) on page 95. Applicants respectfully request the entry of this correction.

25 On page 15 of the specification as filed the term "cyclobutyl" was inadvertently included in the definition of alkyl as "acyclic alkyl chain". Since the term "cyclobutyl" is a cyclic alkyl chain and not an acyclic alkyl chain, the said term is deleted from the definition of acyclic alkyl chain and is included appropriately under the definition of cyclic alkyl chain in the subsequent paragraph by this rectification. Applicants respectfully request the entry of this correction,

30

On page 38 of the specification as filed the structure **I-C1-FD10** was inadvertently presented incorrectly. The experimental procedure for **I-C1-PD10** described on pages 149-150, Example 12, in which SJM and cetirizine dihydrochloride react, can yield only the compound having the structure of I-C1-JtøtøO with a para-chloro phenyl group as presented by this rectification. Accordingly, the correct structure for **I-C1-PD10** has been introduced on page 38 in the specification. Applicants respectfully request entry of this correction.

On page 40 of the specification as filed the product **I-A1-PD18**, described in the Example 32 on pages 156-157 was inadvertently omitted. The experimental procedure for **I-A1-PD18** described on pages 156-157, Example 32, can yield only the compound having the structure of **I-A1-PD18** as presented in this rectification. Accordingly, Applicants respectfully request entry of **I-A1-PD18** in the collection.

On page 44 and 215 of the specification as filed the structure **I-H1-PD14** presented is an incorrect structure and does not correspond to the description presented in the Example 39 on page 172. It is a duplication of structure **I-H1-PD1** and is redundant, while the structure relevant to the Example 39 was inadvertently omitted. The Example 39 on page 161 describes synthesis of **I-H1-PD14**, as shown in the scheme 14, method C, on page 134, using the starting material LI-2c.TFA (LI-2c in presence of trifluoroacetic acid (TFA)) which has a BOC protected *NiF* group, which after BOC removal, couples with the starting derivative having a leaving group (LG) to form an amide derivative, the product **I-H1-PD14**. Accordingly, the correct structure of **I-H1-PD14** has been introduced on pages 44 and 227 (corresponding to page 15 for claims) (claim 14). Accordingly, Applicants respectfully request entry of this correction.

25

On page 49 of the specification and page 216 of claims, the structure of **I-A1-NOPD6** was inadvertently presented incorrectly. The experimental procedure for **I-A1-NOPD6** described on page 185-186, Example 105, which freshly generated formyl chloride of LI-1b and compound **Ib** react, can yield only the compound having the structure of **I-A1-WOPD6** with S=O group adjacent to the imidazole and a "CHa" group adjacent to pyridine ring as

30

presented by this rectification. Accordingly, Applicants respectfully request entry of this correction.

On pages 51 and 217 of the specification as filed, the product, **I-H1-NOPD11**, described in the Example 117, was inadvertently omitted. The experimental procedure for **I-HI-NOPDU** described on page 189, Example 117, can yield only the compound having a structure of **I-H1-NOPD11** as introduced by this rectification. Accordingly, Applicants respectfully request the entry of this correction.

On page 61 of the specification as filed, the structure of **I-CA-MPD22** was an inadvertent repeat of **I-CA-MPD5**, while the correct structure was inadvertently omitted. The structure of **I-CA-MPD22** presented in this rectification is the only possible product described in the Example 73 on page 174, in which nicotiny chloride hydrochloride reacts with **I-A1-PD8**. Accordingly, Applicants respectfully request the entry of this correction.

On pages 106, 119 and 121 of the specification as filed, the phrase "NO-releasing" was inadvertently introduced while combining the two priority provisional applications. The present application combines the subject matter of both the provisional applications and accordingly the invention is broader in scope than the invention presented in any individual provisional application. It is appropriate to use "compounds of formula I" or "prodrugs" in place of "NO-releasing prodrugs". Support for the rectification is found throughout the specification and, for example, on page 23, lines 20-22 and in the list of candidate drugs on pages 106-120. Accordingly, Applicants respectfully request the entry of these corrections.

On page 173 of the specification as filed, the reactant used was inadvertently presented as **I-S12-PD2**, which should read "BOC deprotected **I-S12-PD2**." In fact, BOC containing **I-S12-PD2** was deprotected to react with nicotiny chloride to obtain the product **I-CA-MPD18** in the Example 70. Accordingly, Applicants respectfully request the entry of this correction.

On page 197 of the specification as filed, inadvertently, erroneous ¹H NMR data was provided for I-AX-NOPD₁ which is inconsistent with its structure. Accordingly, Applicants respectfully request the entry of this correction.

5 Claim 1 has been rectified to recite "or novel intermediates in preparation thereof", for which support can be found throughout the specification and, for example, pages 71-73*. Accordingly, Applicants respectfully request the entry of this correction.

10 No new matter has been added by this editorial rectification. Favorable consideration and entry of all the rectifications prior to publication is respectfully requested.

Respectfully submitted,

15 Dated: January 25, 2006


X[^] Vyu^uJvy

Suresh Vepachedu
US Registration No. 46,395

20 Vepachedu Professional Corporation
1230 Georgetown Way
Vestno^π HiUs, IL 60061
(847) 883-0910 (phone)
(847) 883-8659 (Fax)

25 SV
Enclosure
Cc: IB WIPO

PRODRUGS CONTAINING NOVBt BIO-CLEAVABLE LINKERS

This application takes priority from US Provisional Application USSN: 60/604,632 filed 26 August 2004 and Indian Provisional Application 779MUM/200S
 5 filed. 01 July 2005 and are herein incorporated in their entirety.

Field of the Invention

The present invention relates to compositions of prodrugs, including NO-releasing prodrugs, codrugs, double prodrugs and mutual prodrugs, containing bio-labile linkers and linkages, processes for their preparation and pharmaceutical compositions containing
 10 them and their use

Background of the Invention

A prodrug is an active drug chemically transformed into a *per se* inactive derivative which by virtue of chemical or enzymatic attack is converted to the parent drug within the body before or after reaching the site of action. The process of converting an
 15 active drug into inactive form is called drug latention. Prodrugs can be carrier-linked-prodrugs and bioprecursors. A carrier-linked prodrug results from a temporary linkage of the active molecule with a transport moiety. Such prodrugs are less active or inactive compared to the parent active drug. The transport moiety will be chosen for its non-toxicity and its ability to ensure the release of the active principle with efficient kinetics.
 20 Whereas the bioprecursors result from a molecular modification of the active principle itself by generation of a new molecule that is capable of being a substrate to the metabolizing enzymes releasing the active principle as a metabolite,

Prodrugs are prepared to alter the drug pharmacokinetics, improve stability and solubility, decrease toxicity, increase specificity, and increase duration of the pharmacological effect of the drug. By altering pharmacokinetics the drug bioavailability
 25 is increased by increasing absorption, distribution, biotransformation, and excretion of the drug. Limited intestinal absorption, distribution, fast metabolism, and toxicity are some of the causes of failure of drug candidates during development. Avoidance of these foreseeable or proven pharmacokinetic defects thus assumes considerable significance in
 30 drug research. Accordingly, prodrugs play a significant role in drug research as well.

In designing the prodrugs, it is important to consider the following factors: a) the linkage between the carrier and the drug is usually a covalent bond, b) the prodrug is inactive or less active than the active principle, c) the prodrug synthesis should not be expensive, d) the prodrug has to be reversible or a reversible derivative of the drug, and
 5 e) the carrier moiety must be nontoxic and inactive when released.

Prodrugs are usually prepared by: a) formation of ester, hemiesters, carbonate esters, nitrate esters, amides, hydroxamic acids, carbamates, imine, Mannich bases, and enamines of the active drug, b) functionalizing the drug with ester, glycoside, peptide, and other functional groups, c) use of polymers, salts, complexes, phosphoramides, acetals, hemiacetals, and ketal forms of the drug. For example, see Andrejus Korolkovas's,
 10 "Essentials of Medicinal Chemistry", pp. 97-118.

The discovery and characterization of endothelium-derived nitric oxide (NO) was the subject of the 1998 Nobel Prize in Medicine and Physiology. NO is a major signaling molecule with important biological roles. See, for example, Kerwin, Jr., J. F. et al., J. Med. Chem. 1995, 38, 4343, and Williams, R. J. P., Chem. Soc. Rev., 1996, 77. The
 15 major biological functions of NO include controlling blood pressure, smoothing muscle tone and inhibition of platelet adherence and aggregation* assisting the immune system in, destroying tumor cells and intracellular pathogens and participating in neuronal synaptic transmission. See, for example, Mocada, S. et al., Pharmacol. Rev. 1991, 43, 109; Bredt, P.S. et al., *tow.* Rev. Biochem., 1994, 63, 175; Schmidt H. H. W. et al., Cell 1994, 78, 919; Földman, F. L. et al., Chem. and Eng. News. 1993, 71 (20th December issue), 26; and Wilson E. K. Otem. and Ettg. News. 2004 (5* March issue), 39. Endogenously,
 20 NO is produced from arginine by the catalytic action of nitric oxide synthase. See, for example, Nathan, C. et al., Cell 1994, 78, 915, and Marietta, M. A., Cell 1994, 78, 927.

NO is a free radical as well as a scavenger of free radicals. NO reacts quickly with ubiquitously generated reactive oxygen species (ROS) such as superoxide (O₂⁻) to generate a nefarious peroxynitrite (ONOO⁻) molecule, which is implicated in many human diseases such as diabetes, heart disease, Alzheimer's disease and multiple sclerosis. In this setting, NO is often viewed as pathogenic. However, the chemistry of
 25 NO can also be a significant factor in lessening the injury mediated by reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS). There is a relationship

between NO and oxidation, nitrosation and nitration reactions. A number of factors determine whether NO promotes, abates or interconnects these chemistries. See, for example, Espay, *et al.*, A chemical perspective on the interplay between, NO, reactive oxygen species, and reactive nitrogen oxide species, *Ann N. Y. Acad. Sci.* 2002, 962, 195.

Thus* by being a free radical along with the ability to scavenge other free radicals, NO is placed in a pivotal regulatory position. Insight into these pathophysiological processes and signaling are highly relevant to develop therapeutics.

NO deficiency has been implicated in the genesis and evolution of several disease states. In patients with cardiovascular problems, the production of superoxide is increased and level or location of NO synthesis is disrupted thereby causing cellular dysfunction as a result of vasoconstriction of blood vessels, which can lead to, if prolonged, cell damage or death. Agents that act to maintain the normal balance between NO and superoxide in vascular endothelial cells may prove particularly useful in this regard. See, for example, Stokes, K., *et al.*, *Free Radic. Bio. Med.*, 2002, 33, 1026-1036.

Nutritional and pharmacological therapies that enhance the bioactivity or production of NO have been shown to improve endothelium-dependent vasodilation, reduce symptoms, and slow the progression of atherosclerosis. Some of the strategies for NO modulation encompass anti-inflammatory, sexual dysfunction, and cardiovascular indications. Apart from newly developed drugs, several commonly used cardiovascular drugs exert their beneficial action* at least in part, by modulating the NO pathway. Pharmacological compounds that release NO have been useful tools for evaluating the pivotal role of NO in cardiovascular physiology and therapeutics, NO-DONORS;

There are a wide variety of structurally dissimilar organic compounds that act as NO donors and release NO in solution. Some NO donors, such as isosinyl nitrite, nitroglycerine (GTN) and sodium nitroprusside, have been used in cardiovascular medicine long before their biochemical mechanism was understood. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through activation of guanylate cyclase with subsequent formation of cGMP. The relative importance of enzymatic versus non-enzymatic pathways for NO release, the identity of

the actual NO-generating enzymes and the existence of competing metabolic events are additional important determinants of the different NO donor classes. Pharmacological compounds that release NO constitute two broad classes of compounds: those that release NO or one of its redox congeners spontaneously and those that require enzymatic metabolism to generate NO. See, for example Ignatko, L. J. et al., Nitrite oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview, Circ. Res. 2002, 90, 21-28.

Nitroglycerin/glycerol trinitrate (GTN) and compounds referred to as nitrovasodilators or NO donors are frequently used in the treatment of ischemic heart disease. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through activation of guanylate cyclase with subsequent formation of sGMP. However, early development of tolerance to nitrate therapy, particularly during acute myocardial infarction, has been the clinically significant drawback with GTN and some of the other available organic nitrates. This is a significant clinical problem and there exists a need for novel nitrate-based anti-anginal agents, which do not cause the problem of nitrate tolerance.

There are a number of new examples of organic nitrates in which an alkyl or aralkyl mononitrate is covalently linked to an existing drug molecule. Existing drugs from a large number of therapeutic areas such as anti-inflammatory, antiallergic, antibiotic, anticancer, antidiabetic, antiviral, antihypertensive, antianginal, anticonvulsant, analgesic, antiasthmatic, antidepressant, antidiarrheal, antiarrestive, antimigraine, antipsychotic, antipyretic, antilulcerary, antithrombotic, etc., were made and evaluated. Some of Nicox's patents include; Synthesis and evaluation of nitrooxy derivatives of NSAIDs (WO 94*2463, WO 0230867, WO 0292072, WO 0313499 and WO 0384550), aspirin (WO 9716405, WO 0044705 and WO 0104082), paracetamol (WO 002584 and WO 0230866), antiepileptic agents (WO 0300642 and WO 0300643), COX-2 inhibitors (WO 0400781 and WO 0400300), statins (WO 04105754), ACE inhibitors (WO 0400432 and WO 04106300), and of known drugs used for the treatment of disease conditions resulting from oxidative stress and endothelial dysfunction (WO 0061537).

Most of these nitrate esters were shown to possess not only superior or equal efficacy when compared to the original drug but also exhibit much-reduced side effects. In fact, because of their superior efficacy combined with reduced toxicity, a few of such nitrate ester-containing drug conjugates are successfully passing through various stages of clinical trials. Some of Nicox's nitrooxy derivatives of drugs which are in clinical trials include: NCX 4016 (Phase II, peripheral vascular diseases), NCX 701 (Phase II, Acute pain), HCT 1026 (Phase I, Alzheimer's disease), HCT 3012 (Phase II, Osteoarthritis), NCX 285 (JND, Osteoarthritis), NCX 1022 (Phase IIa completed, Dermatitis), NCX 1020 (Phase I, Asthma/COPD), NCX 1000 (Phase I, Portal hypertension), and NCX 1510 (Phase II, Allergic rhinitis).

US5767134 and US20050002942A1 disclosed a few disulfide-containing drug conjugates. WO 9842661, US 5807847, WO 0054756 and WO 0149275 reported a few nitrooxy derivatives of organic molecules containing a hydroxyl or disulfide group which are called "SS-nitrates". These references are incorporated herein by reference.

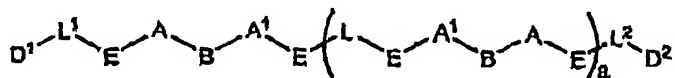
Representative examples from WO 9842661 have shown superior vasorelaxant activity and no tolerance was observed to the pGMP-inhibitory effects of those compounds under the same experimental conditions used for the induction of in vivo tolerance. WO 0149275 reports drug conjugates where an inflammatory drug is covalently linked to the β -thio-nitrate via an ester bond. Biotransformation pathways proposed for NO release from GTN have largely been hemocysteine-dependent or sulfhydryl-dependent. See, for examples, Thatcher, G. R. J. et al., Chem. Soc. Rev. 1998, 27, 331 and reference cited thereto, and Bennett, B. M. et al., Trends Pharmacol. Sci. 1994, 15, 245. These references are incorporated herein by reference.

A mutual prodrug is the association in a unique molecule of two drugs, usually synergistic, attached to each other, one drug being the carrier for the other and vice versa. The embodiments of the invention also provide mutual prodrugs, which are prodrugs of two or three therapeutic agents currently used/potential for use in combination therapy utilizing novel bio-cleavable linkers, water-soluble prodrugs of insoluble/lipophilic-soluble therapeutic agents using the same linker technology and water-soluble double and

triple prodrugs of sparingly-soluble therapeutic agents or any of the prodrugs linked to NO-releasing agent using the same linker technology.

Summary of the Invention

- Present invention relates to prodrugs of formula (I) or pharmaceutically acceptable salts thereof;



Formula (I)

wherein,

a is 0-2;

- 10 B independently represents a bond, $(CH_2)_b$, $(CH_2CH_2O)_c$, S-S, S-SK, S-SO₂ or S-S=NH; b is 1-6; c is 0-4;

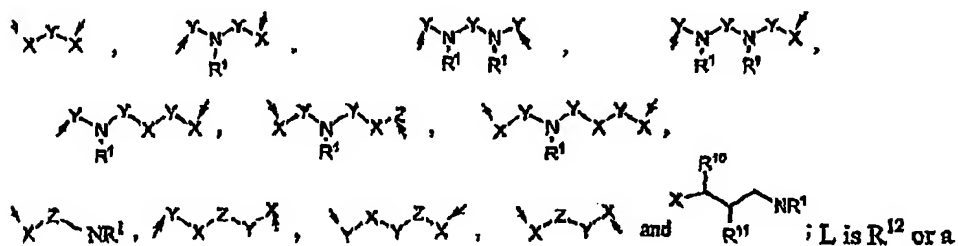
A and A¹ independently represent a bond, $(CH_2)_d$, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

d is 1-8;

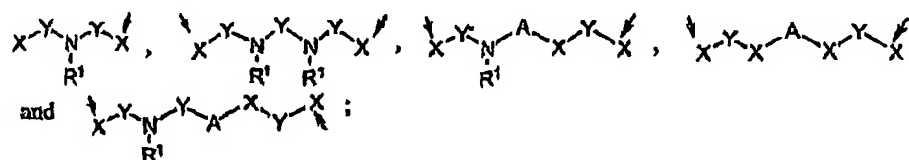
- 15 D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OCC(O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹)C(O)NHR¹ and -N(R¹)C(=O)NHR¹; D² independently represents D¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, N₂, a linkable nitric oxide-releasing group comprising a NONOate, a group comprising one or more of water-solubilizing functional groups, or a polymer;

E independently represents C=O or a bond;

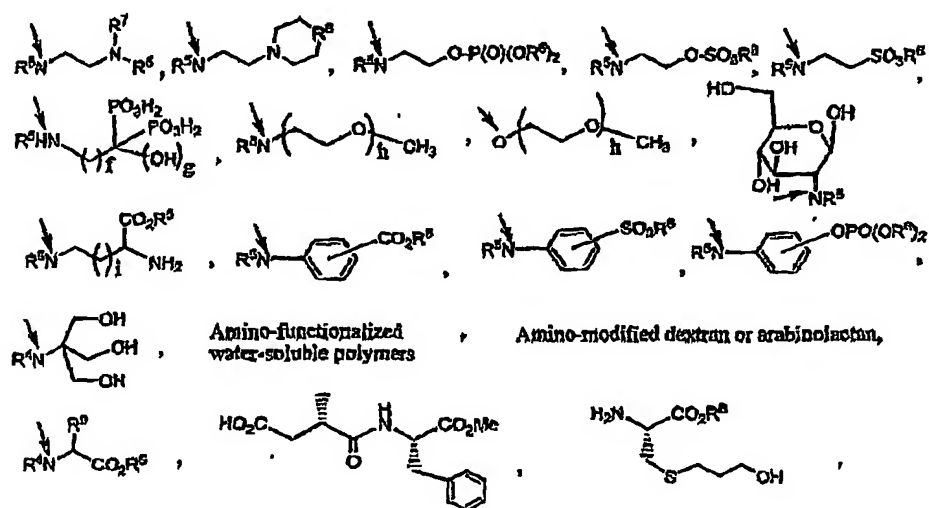
L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:

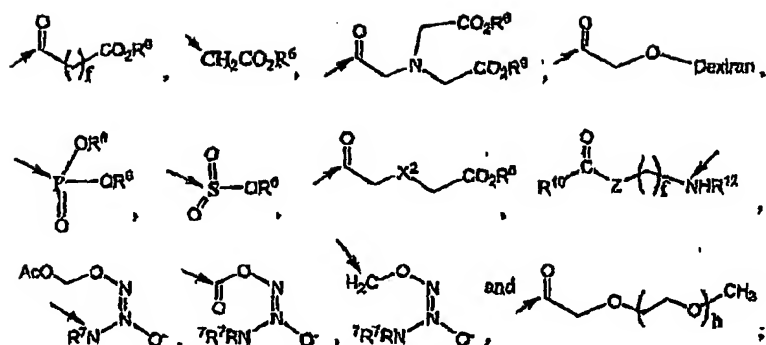


- 25 group with bonding in any direction independently selected from the group consisting of



- 5 X independently represents a bond, C, O, S, or NR^1 ;
Y independently represents a bond, $\text{C}=\text{O}$, $\text{C}=\text{S}$, $\text{S}=\text{O}$, SO_2 , $\text{P}(=\text{O})\text{XR}^1$, or $(\text{CH}_2)_4$;
Z independently represents a bond, or $(\text{CH}_2)_j$; wherein, j is 1-4;
 R^1 independently represents a bond, H, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_5\text{-C}_{14})\text{aryl}$, aralkyl or M^{++} ;
 R^2 independently represents H, NH_2 , or NHAc ;
10 R^3 independently represents H, CO_2R^4 , $\text{CH}_2\text{CO}_2\text{R}^4$,
 R^4 independently represents H, OH, $\text{O}(\text{C}_1\text{-C}_8)\text{alkyl}$, OM^{++} , or a group selected from the group consisting of:

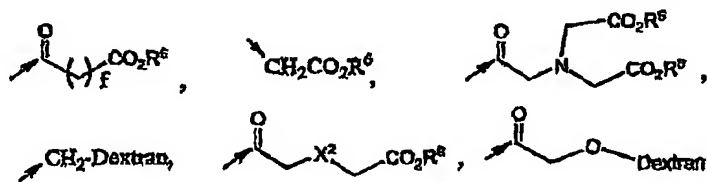




M independently represents Na, K or a pharmaceutically acceptable metal ion,

e = 1-3,

- 5 R⁵ independently represents at each occurrence H, M⁺, (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, substituted (C₁-C₈)alkyl, hetero(C₂-C₄)alkyl, CC(=O)CC(=O)CHR⁵, CH₂C(=O)OR⁵, P(=O)(OR⁵)₂,



X² independently represents O, S, SO, SO², or NR⁵;

R⁶ independently represents H, Na⁺, K⁺, any other pharmaceutically acceptable metal ion,

- 10 (C₁-C₈)alkyl or (C₃-C₈)cycloalkyl,

R⁷ independently represents at each occurrence same or different R⁵;

R⁸ independently represents CH₂, O, NR⁴, S, S=O or O=S=O;

R⁹ independently represents H, (C₁-C₈)alkyl or an amino acid;

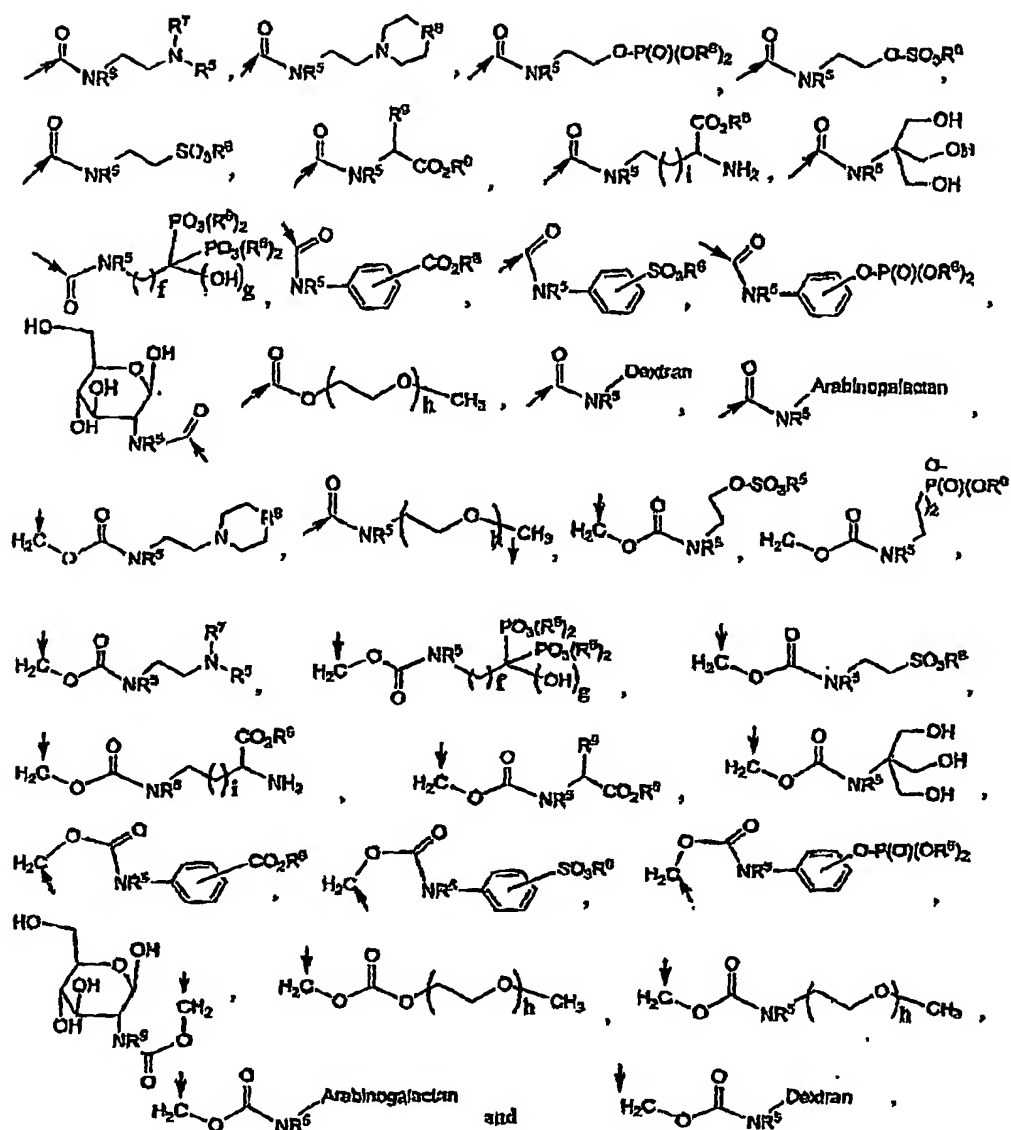
f is 0-6;

- 15 g is 0-1;

h is 1-2000;

i is 1-4;

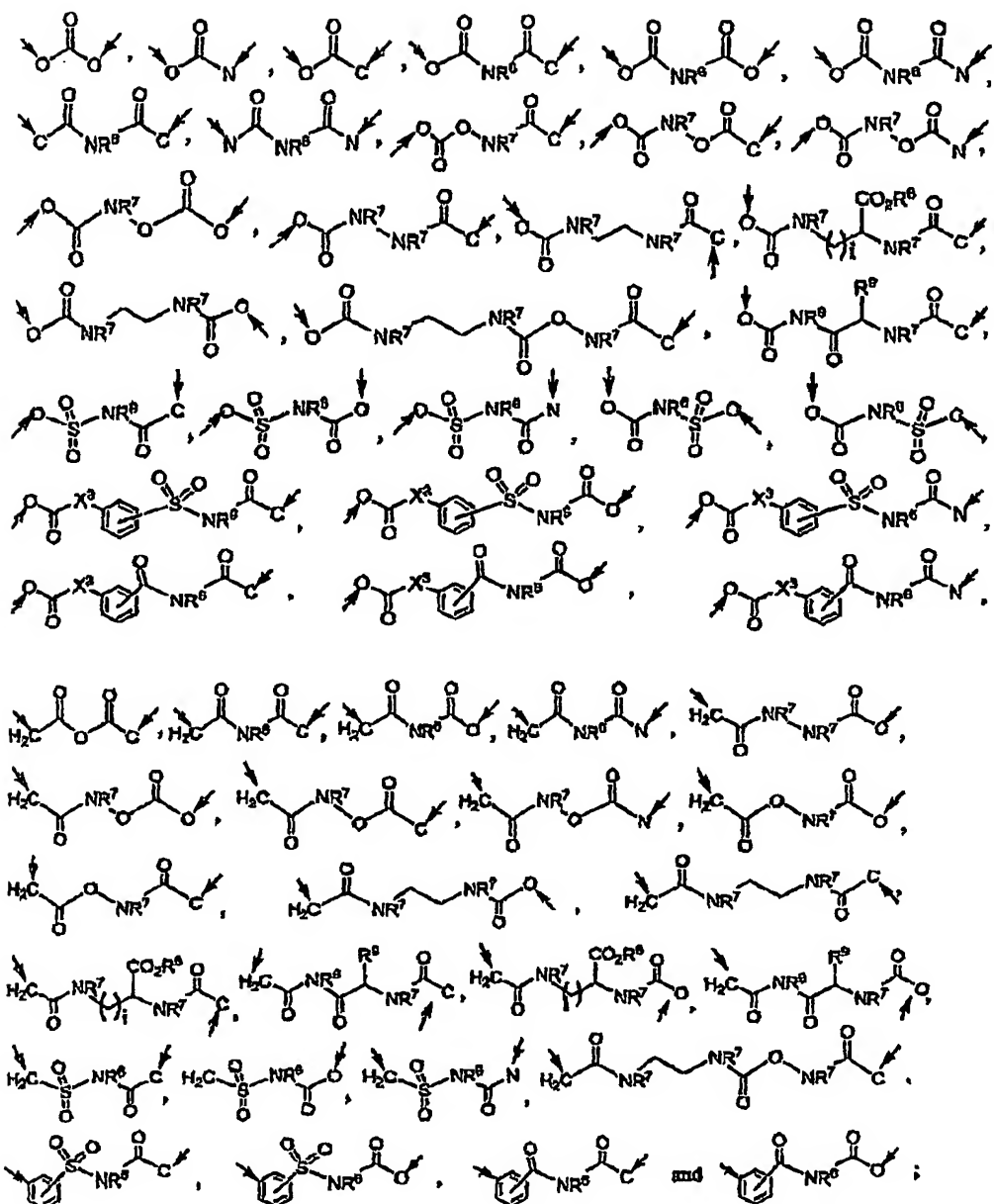
R¹⁰ and R¹¹ independently represent H, (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl or a group selected from the group consisting of:



With a proviso that when R¹⁰ is selected from the above group, Rⁿ represents H or (C_j-C₈)alkyl, and when R¹¹ is selected from the above group, R¹⁰ represents H or (C_i-

5 C₈)aftyI;

R^{12} independently represents a group selected from fha group consisting of;



5 and X³ is independently O or NR⁷.

Another embodiment of the invention is a pharmaceutical composition comprising one or more compounds of formula I or intermediates thereof and one or

more of pharmaceutically acceptable carriers, vehicles or diluents. Further embodiments include methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula I

Detailed Description of the Invention

5 The present invention characterizes compositions, methods of preparation and methods of use of prodrugs, NO-releasing prodrugs, mutual prodrugs, double prodrugs, and prodrugs.

10 The compounds of the present invention are prodrugs or mutual prodrugs in which known therapeutic agents or potential therapeutic agents are linked covalently to novel cleavable linkers.

15 The compounds of the present invention also include NO-releasing prodrugs in which a therapeutic agent is linked covalently to nitrooxy (nitrate ester) group via a novel bio-cleavable linker containing a strategically placed disulfide group at β -position to the nitrate ester. The present invention also characterizes composition of NO-releasing prodrugs (i.e., nitrooxy ester or nitrate ester prodrugs), processes for their preparation, pharmaceutical composition containing them and their use.

20 Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Listed below are definitions of various terms used to describe the compounds of the present invention. These definitions apply to the term as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or part of a larger group.

25 The term "amino-containing" refers to drug/carrier molecule with NH functional groups such as amino (both primary and secondary), amide, urea, sulfonamide, carbamate, phosphoramidate, isulfamate, hydrazone, semicarbazone, thiosemicarbazone, hydrazide, carbazate and the like. This also includes NH-containing heterocyclic compounds such as imidazoles, benzimidazoles, pyrazoles, benzopyrazoles, pyrroles, indoles, triazoles, tetrazoles, benzotriazoles, benzotetrazoles and their derivatives. These NH-containing heterocyclic compounds can be sub-structures of more complex drug/carrier molecules. Amino group of the candidate drug can be primary or secondary

30

(both acyclic and cyclic) which include amide-NH, sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazide-NH, hydrazone-NH, semicarbazone-NH, thiosemicarbazone-NH, urea-NH and also drugs containing indole, imidazole, benzimidazole, thiazole, oxazole, pyrrole, pyrazole, triazole, tetrazole, or similar >NH-containing heterocyclic substructures of a more complex drug molecule,

The term "hydroxyl-containing" refers to drug molecules with hydroxyl groups (primary, secondary, tertiary and phenolic) including hydroxyl groups of hydroxamic acids and ketoximes derived from keto-containing molecules. Hydroxyl group of drugs can be of primary, secondary, tertiary or phenolic nature.

The term "thiol-containing" refers to drug molecules with thiol (SH) group.

The term "halo" refers to fluoro, chloro, bromo, and iodo.

The term "halide" refers to fluoride, chloride, bromide and iodide.

The term "alkyl" refers to acyclic alkyl chains. For example, the term "C₁-C₈ alkyl" refers to methyl, ethyl, propyl, isopropyl, butyl, s-butyl, and t-butyl, pentyl, hexyl, octyl, and the like.

The term "cycloalkyl" refers to cyclic alkyl chains, e.g., the term "C₃-C₈ cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "aryl" refers to phenyl and the like.

The term "alkyl" refers to methyl, ethyl and the like.

The term "alkoxy" refers to both acyclic and cyclic C₁-C₈ alkoxy. For example, the term "C₁-C₈ alkoxy" refers to methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, butoxy, cyclobutoxy, s-butoxy, and t-butoxy, cyclopentyl, pentyloxy, hexyloxy, cyclohexyloxy, heptyloxy, cycloheptyloxy, octyloxy, cyclooctyloxy and the like.

The term "heterocyclic" and "heteroaryl" refers to both saturated and unsaturated 5- and 6-membered rings (including benzofused) containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Any of these rings may be substituted with up to three substituents independently selected from the group

consisting of amino, halo, alkoxy, alkyl, cyano, nitro, hydroxyl, sulfhydryl, carboxyl and the like. Saturated rings include, for example, pyrrolidine, piperidine, piperazine, tetrahydrofuryl, oxazolidinyl, thiazolidyl, pyran, and the like. Benzofused saturated rings include indolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl and the like. Unsaturated rings include furanyl, thienyl, pyridinyl, pyrrolyl, N-ethylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, tetrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, furazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, and the like. Benzofused unsaturated rings include isochroman-5-yl, benzoxazolyl, benzthiazolyl, quinolyl, benzofuranyl, thionaphthyl, indolyl and the like.

10 The term "substituted alkyl" refers to acyclic and cyclic alkyl groups substituted with one or more of groups such as alkyl, aryl, hydroxy, alkoxy, cyano, carboxyl, sulfhydryl, alkylthio, amino, nitro, halo, carbonyl, carbamate, sulfamate, sulfonate, sulfato, and the like.

15 The term "substituted aryl" refers to aryl groups substituted (including fused) with one or more of groups such as alkyl, aryl, hydroxy, alkoxy, cyano, carboxyl, sulfhydryl, alkylthio, amino, nitro, halo, carbonyl, carbamate, sulfamate, sulfonate, sulfato, and the like.

20 The term "amino acid" refers to molecules containing one or more amino and carboxyl groups. Examples of alpha-amino acids (D-, L- and DL- amino acids) include natural alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. Other examples include beta-amino acids and known natural amino acids.

25 The term "amino acid ester" as used in this specification refers to an amino acid where the carboxyl group is substituted with an alkyl group. That is, the alkyl group when taken together with the carboxyl group forms an alkyl ester. It is appreciated that some amino acids (eg., aspartic acid and glutamic acid) have two carboxyl groups these may form mono- and diesters.

30 The term "protecting group" (PG) refers to an 'amino protecting group' or a 'hydroxyl protecting group' or a 'carboxyl protecting group' and the like.

The term "amino protecting group" refers to a group that selectively blocks or protects the amino functionality in presence of other functional groups on the molecule. Examples of such amino-protecting groups include the formyl group, the trityl group, the phthaloyl group, the acetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, the carbamate-type blocking groups such as benzyloxycarbonyl ("CBZ"), 9-fluorenylmethoxycarbonyl ("Fmoc"), tert-butoxycarbonyl ("BOC"), trichloroethylcarbonyl and the like. Additional examples of amino protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1991. Molecules with two or more amino groups may form mono-, di-, tri-, poly-, protected derivatives depending on the reaction conditions used.

The term "hydroxyl protecting group" refers to a group that selectively blocks or protects hydroxyl functionality in presence of other reactive functional groups on the molecule. Examples of such hydroxyl-protecting groups include, for example, ether groups including methyl and substituted methyl ether groups such as methyl ether, methoxymethyl ether, methylethyl ether, tert-butyl ether, tetrahydropyranyl (THP), (phenyldimethylsilyl)methyl ether, benzyloxymethyl ether, p-methoxybenzyloxymethyl ether, and tert-butoxymethyl ether; substituted ether groups such as ethoxyethyl ether, 1-(2-chloroethoxy)-ethyl ether, 2,2,2-trichloroethoxyethyl ether and 2-(trimethoxy)ethyl ether; isopropyl ether groups; phenyl and substituted phenyl ether groups such as phenyl ether, p-chlorophenyl ether, p-methoxyphenyl ether, and 2,4-dimethoxyphenyl ether, benzyl and substituted benzyl ether groups such as benzyl ether, p-methoxybenzyl ether, o-nitrobenzyl ether, and 2,6-dichlorobenzyl ether; and alkyl ether groups such as isopropyl-, tert-butyl- and tmsopropyl ethers, mixed alkylsilyl ether groups such as diisopropylsilyl ether, tert-butyl dimethylsilyl ether and diisopropylsilyl ether; and ester protecting groups such as acetate ester, formate ester, benzylformate ester, mono-, di-, and trichloroacetate esters, pivalate ester, phenoxyacetate ester, and p-chlorobenzyloxyacetate, benzyloxycarbonate, 9-fluorenylmethyl carbonate, tert-butoxycarbonate, triethoxyethyl carbonate, carbamate, sulfonate and the like. Additional examples of hydroxyl protecting groups are described by T. W. Greene, "Protective Groups in

Organic Synthesis", John Wiley and Sons, New York, NY-, 1991. Molecules with two or more hydroxyl groups may form mono- and di-esters/ethers depending on the reaction condition,

5 The term "carboxyl protecting group" refers to a group that selectively blocks or protects carboxyl functionality in presence of other reactive functional groups on the molecule. Examples of such carboxyl-protecting groups include, for example (substituted) alkyl esters such as methyl ester, ethyl ester, t-butyl ester, (substituted) benzyl ester, trichloroethyl ester, and the like. Additional examples of carboxylic acid protecting groups are described by T. W. Greene, "Protective Groups in Organic Synthesis", John
10 Wiley and Sons, New York, N.Y., 1991. Molecules with two or more carboxylic acid groups may form mono-, di-, tri-, tetra-, poly-protected derivatives depending upon the reaction conditions used.

The term "carboxyl activating group" refers to a leaving group ("LG") of a carboxylic derivative that is easily replaced by an incoming nucleophile. Such "LG" groups include, but are not limited to, (substituted) alkoxy, acyloxy, nitrogen containing unsaturated heterocycles such as N-oxybenzotriazole, imidazolyl, o/p-toluenephenoxy, pentachlorophenoxy, N-oxy-succinimide, N,N'-dicyclohexylisourea-O-yl, N-hydroxy-N-methoxyamino, and the like; acetates, formates, sulfonates such as p-toluenesulfonate, p-toluenesulfonate, benzotriazolesulfonate or p-toluenesulfonate, and the like; and halides especially fluoride, chloride, bromide, or iodide.
15 20

The term "carbonyl activating reagent" refers to a reagent that converts the carbonyl of a carboxylic acid group into one that is more susceptible to nucleophilic attack and includes, but is not limited to, such reagents as those found in "The Peptides", Gross and Mendenhofer, Eds., Academic Press (1979), Ch. 2, and M. Bodansky, "Principles of Peptide Synthesis", 2nd Ed., Springer-Verlag Berlin Heidelberg, 1993, hereafter referred to as "The Peptides" and "Peptide Synthesis" respectively. Carbonyl group (i.e., aldehyde or keto group) of candidate drugs may be converted first to an aldol, ketone, hydrazone, semicarbazone and the like, before coupling to the linker. Specifically, carbonyl activating reagents include thionyl chloride, thionyl chloride, oxalyl chloride, and the like; esters of alcohols such as nitrophenol, pentachlorophenol and the like; and compounds such as 1'-carbonyldiimidazole (CDI),
25 30

1,2,4-triazole, imidazole, N-hydroxysuccinimide, dicyclohexylcarbodiimide, EDC₃ phosgene or its equivalents, N,N-dimethylaminopyridine (DMAP) and the like.

The terms "phosgene or its equivalents" refer to phosgene or its equivalents such as diphosgene, triphosgene, CDI, PSC, BTBC, alkoxycarbonyl chlorides, o/p-Ritrosubstituted phenoxycarbonyl chlorides, and the like.

In general, the term "pharmaceutically acceptable" when used as an adjective means substantially non-toxic to living organisms.

The terms "pharmaceutically acceptable metal ions or salts" refer to salts of the compounds of this invention, which are substantially non-toxic to living organisms. See, e.g., Berge, S. M. et al, "Pharmaceutical Salts", J. Pharm. Sci., 66:1, 1977. Typical pharmaceutical salts include those salts prepared by reaction of the compounds of this invention with an inorganic or organic acid or base. Such salts are known as acid addition or base addition salts respectively. These pharmaceutical salts frequently have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions. Examples of pharmaceutically acceptable salts are those with inorganic bases such as sodium, potassium, calcium, magnesium, and hydroxides, and the like, or with organic bases such as lysine, arginine, triethylamine, diethylamine, piperidine, and the like.

The term "suitable solvent" refers to a solvent that is inert to the ongoing reaction and sufficiently solubilizes the reactants to effect the desired reaction. Examples of suitable solvents include but are not limited to, dichloromethane, chloroform, 1,2-dichloroethane, diethyl ether, tert-butyl methyl ether, acetonitrile, ethyl acetate, 1,3-dimethyl-2-imidazolidinone, tetrahydrofuran, dimethylformamide, benzene, toluene, xylene, N-ethylacetamide, N-methylpyrrolidone, chlorobenzene, dimethylsulfoxide, diethoxyethane, water, methanol, ethanol, isopropanol, pyridine, acetonitrile, mixtures thereof and the like.

The term "suitable base" refers to a base, which acts as a proton trap for any protons, which may be produced as a byproduct of the desired reaction, or to a base, which provides a reversible deprotonation of an acidic proton from the substrate and is reactive enough to effect the desired reaction without significantly effecting any undesired reactions. Examples of such bases include but are not limited to, carbonates,

bicarbonates, and hydroxides (e.g., lithium, sodium, potassium, magnesium, calcium, and the like), sodium/potassium/calcium, hydride, sodium/potassium alkoxide (i.e., methoxide, ethoxide, tert-butoxide and the like), triethylamine, isopropylethylamine, N-methylpyrrolidine, N-methylpiperidine, tetramethylguanidine, or aromatic nitrogen containing heterocycles such as pyridine, 4-(dimethylamino)pyridine (DMAP), and the like.

The term "nitric oxide-releasing group" refers to a linkable nitric oxide-releasing group such as $\text{AcOCH}_2\text{CH}_2\text{O-Na-N}(\text{Cr})\text{R}^7$, $\text{OCHOCH}_2\text{-O-N}(\text{OOR}^7)\text{R}^7$, $\text{CH}_2\text{-O-N}_2\text{-N}(\text{OR}^7)\text{R}^7$ and the like.

The term "therapeutic agent" refers to biologically active molecules such as drugs, vitamins, and other molecules, agents or substances concerned with or attributing to the treatment and cure of illness or contributing to the general well being of a mammal or human. The therapeutic agents can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity®-Prous Science Drugs of the Future™, The EMBL® and the like. The Merck Index is a one-volume encyclopedia of chemicals, drugs and biologicals that contains more than 10,000 monographs. Each monograph in this authoritative reference source is a concise description of a single substance or a small group of closely related compounds. Prous Science is an international health science publishing company, established in 1958 and headquartered in Barcelona, Spain. Prous Science Drugs of the Future™, produced by Prous Science Publishers, contains comprehensive drug monographs providing product information on new compounds, including the synthesis and corresponding schemes, pharmacological action, pharmacokinetics and metabolism, toxicity, clinical studies, manufacturing, and references. Information on compounds is continuously updated as advances in development status are disclosed worldwide. The Prous Science Integrity® is a drug R&D portal where knowledge areas are coordinated to provide a harmonious and interrelated whole, which includes Drugs & Biologies, Targets, Organic Synthesis, Experimental Pharmacology, Pharmacokinetics and Metabolism, Clinical Studies, Disease Briefings, Companies & Markets, Utility and Patents. The *investigational Drugs database IDdb*, developed by Thomson Current Contents, is a pharmaceutical competitor intelligence service. It covers all aspects of investigational drug development, from first patent to eventual launch or discontinuation. The Ensemble® on the Web

provides essential information, including chemical structures, on more than 140,000 compounds with demonstrated biological activity in the drug research and development pipeline.

5 The term "vitamin" includes vitamin A, vitamin C, thiamine, folio acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadione, menadiol, and vitamin K5.

The term "peptide" includes large and small peptides, but not limited to, targetable small peptides such as a dipeptide, tripeptide, tetrapeptide, etc,

10 The term "ligand" means a small molecule that binds to a larger macromolecule, whether or not the ligand actually binds at a metal site. Such ligands can be small peptides.

One aspect of the invention is to provide mutual prodrugs of two or three therapeutic agents currently used for use in combination therapy utilizing novel bio-cleavable linkers, water-soluble prodrugs of insoluble and sparingly-soluble therapeutic agents using the same linker technology, and water-soluble double and triple prodrugs of sparingly-soluble therapeutic agents using the same linker technology. The embodiments of the invention may also comprise vitamins and targetable small peptides in addition to or in place of a prodrug to yield targetable prodrugs.

20 The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or from different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with similar mechanism of action or act on different biological targets with different mechanisms of action.

To be considered for prodrug synthesis, the candidate drugs should contain one or more of the essential functional groups such as amino, hydroxyl, keto, or carbonyl groups in their structure.

Any group of the candidate drug can be primary or secondary (both acyclic and cyclic) which include amide-NH, sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazide-NH, semicarbazone-NH, oxime-NH and also drugs containing indole, imidazole, benzimidazole, thiazole, pyrazole, triazole, tetrazole, or similar NH-containing heterocyclic substructures of a more complex drug molecule.

Similarly, hydroxyl group of drugs can be of primary, secondary or tertiary nature. Keto group of candidate drugs may be converted first to ketoxime, hydrazine, semicarbazone and the like, before coupling to the linker. Obviously, hydroxyl or amino functions thus generated will be used to form covalent bond between the drug and the linker.

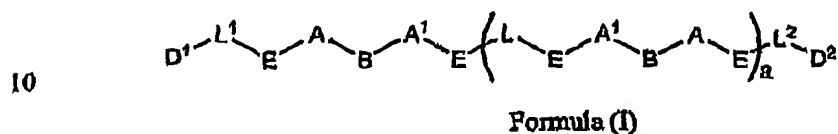
5 The candidates for combining mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (including those combination studies at investigational stage) in various therapeutic areas provided each of those drugs possesses the requisite functional group(s). There are a number of therapeutic areas where such combination therapy is applied routinely and successfully,

10 On the basis of the proposed sulfhydryl-dependent mechanism of NO-release from GTN₃ we have designed the compounds and prodrugs of the present invention where a suitable drug molecule is linked covalently to a nitroxy (nitrate ester) group via a Mo-labile linker containing strategically located disulfide bond at a position to nitrate ester. In vivo, the disulfide bond in the prodrug is expected to be reduced by
 15 endogenous sulfhydryl-containing species such as glutathione (GSH) to generate a reactive thiolate anion (i.e., S⁻-mercaptate), which can trigger further break-down of the linker moiety to release the free drug (via a mechanism as shown Scheme MI) and NO simultaneously at the same location. It is possible, as depicted in the mechanism Scheme MJ, the release of NO can go via a hypothetical cyclic intermediate.
 20 Similar hypothetical mechanism was proposed for NO release from SS-aitates, which we also designed on the basis of a sulfhydryl-dependent NO release from GTN. See, for example, Zavorin, S. I et al., Organic Letters, 2001, 3, U 13, incorporated herein in its entirety. Mutual prodrugs can be made by linking covalently any two of the following:
 25 an amino-containing therapeutic agent to another amino-containing therapeutic agent; an amino-containing therapeutic agent to a hydroxyl-containing therapeutic agent; an amino-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative;
 30 a hydroxyl-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; an amino-containing therapeutic agent to a carboxyl-containing therapeutic agent and its derivative; an amino-containing therapeutic agent to a keto-containing therapeutic agent or its hydrazone, semicarbazone or oxime derivative and the like; a

hydroxyl-containing therapeutic agent to a α -containing therapeutic agent via its hydrazoac, sejoncarbazone, or oxime derivative and the like.

Another aspect of the present invention is to provide new nitrate ester (NO releasing) prodrugs of many types of existing drugs using novel biodegradable linkers. Such prodrugs are expected to exhibit better efficacy and tolerability with reduced side effects compared to the corresponding original drugs.

An embodiment of present invention relates to the compounds of formula (I) or pharmaceutically acceptable salts thereof:



wherein,

a is 0-2;

15 B independently represents a bond, $(CH_3)_6$, $(CH_2CH_2O)_6$, S-S, S-S=O, S-SO₂ or S-S=NH; b is 1-6; c is 0-100;

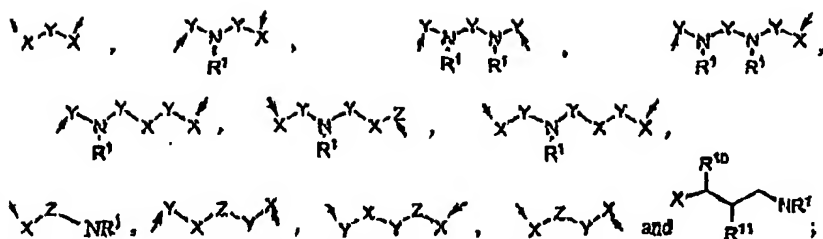
A and A¹ independently represent a bond, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene;

d is 1-8;

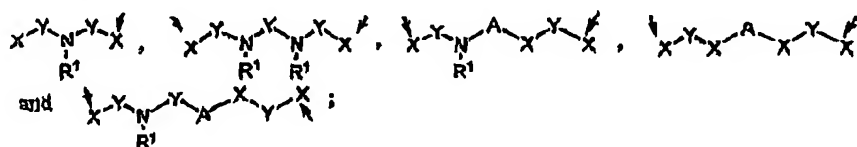
20 D* represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -KHR¹, -CO₂H, -CONHR¹, -OCC(=O)NHR¹, -SO₂NHR¹, -OSO₂NHR*, -N⁺CC⁻M⁺, -R¹ and -N(R¹)SO₂NHR¹; D² independently represents D¹, aptamer, protein, monoclonal antibody, vitamin R², R³, R*, NO, NO₂, a linkable nitric oxide-releasing group comprising a NONOate, a group comprising one or more of water-solubilizing functional groups, or a polymer;

25 E independently represents any of a bond;

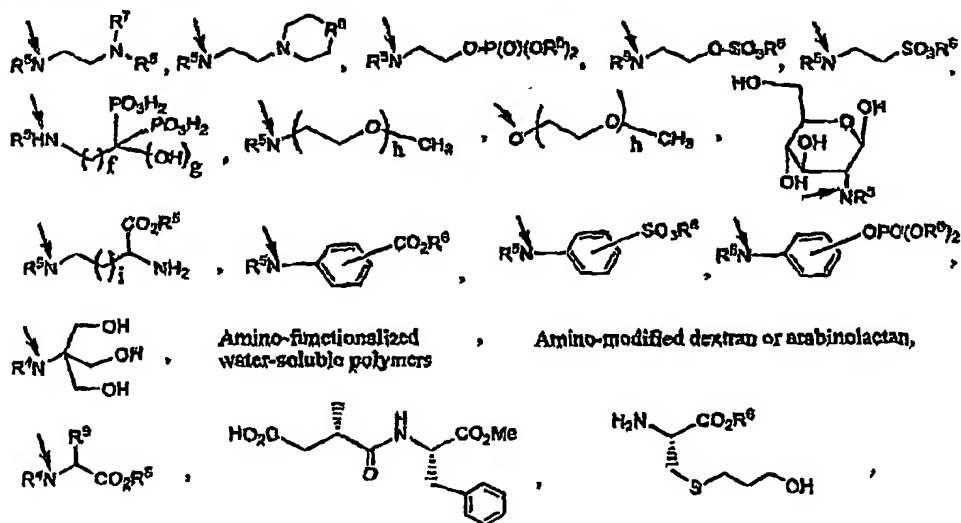
L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:

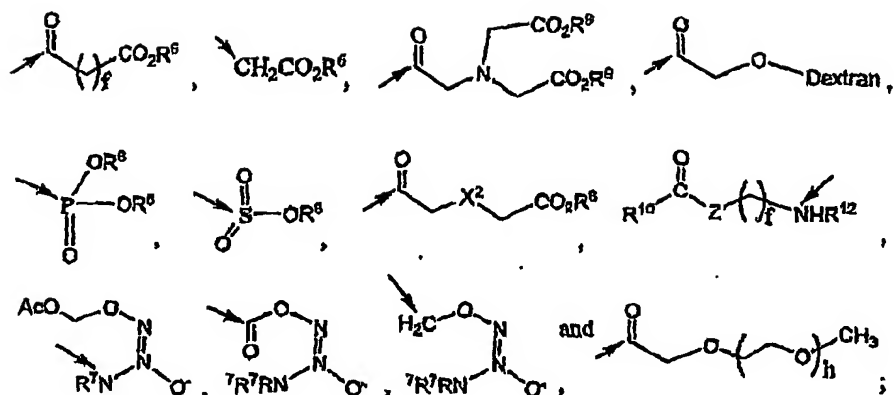


L is \mathbb{R}^{12} or a group with bonding in any direction, independently selected from the group consisting of:



- 5 X independently represents a bond, C, O, S, or NR¹;
Y independently represents a bond, C=O, C=S, S=O, SO₂, P(=O)XR¹, or (CH₂)₄;
Z independently represents a bond, or (CH₂)_j; wherein, j is 1-4;
R¹ independently represents a bond, H, (C₁-C₈)alkyl, (C₃-C₁₄)aryl, aralkyl or M⁺;
R² independently represents H, NH₂, or NHAc;
10 R³ independently represents H, CO₂R⁵, CH₂CO₂R⁵,
R⁴ independently represents H, OH, O-(C₁-C₈)alkyl, OM⁺, or a group selected from the
group consisting of:

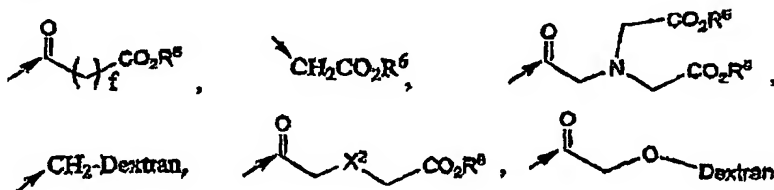




M independently represents Na, K or a pharmaceutically acceptable metal ion,

e = 1-3,

R⁵ independently represents at each occurrence H, M⁺, (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, substituted (C₅-C₁₄)aryl, hetero(C₂-C₁₄)aryl, C(=O)(CH₂)_fCHR⁹CO₂R⁵, CH₂C(=O)OR⁵, P(=O)(OR⁵)₂,



X² independently represents O, S, SO, SO₂, or NR⁵;

R⁶ independently represents H, Na⁺, K⁺, any other pharmaceutically acceptable metal ion,

10 (C₁-C₈)alkyl, or (C₃-C₈)cycloalkyl;

R⁷ independently represents at each occurrence same as different R⁵;

R⁸ independently represents CH₂*O, NR⁴, S, SO or O=SK);

R⁵ independently represents H, (C₁-C₃)alkyl or acyl amino add;

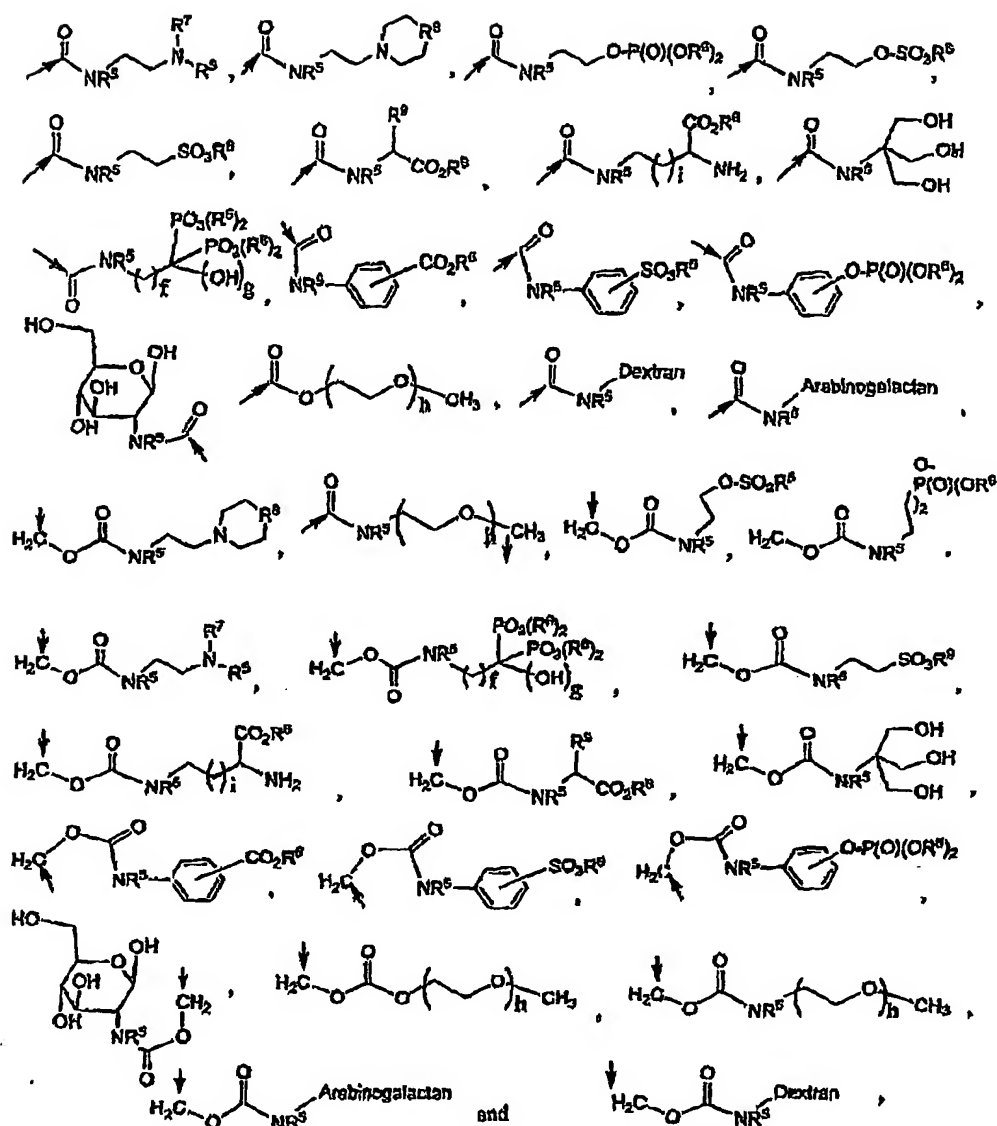
f is 0-6;

15 g is 0-1;

h is 1-2000;

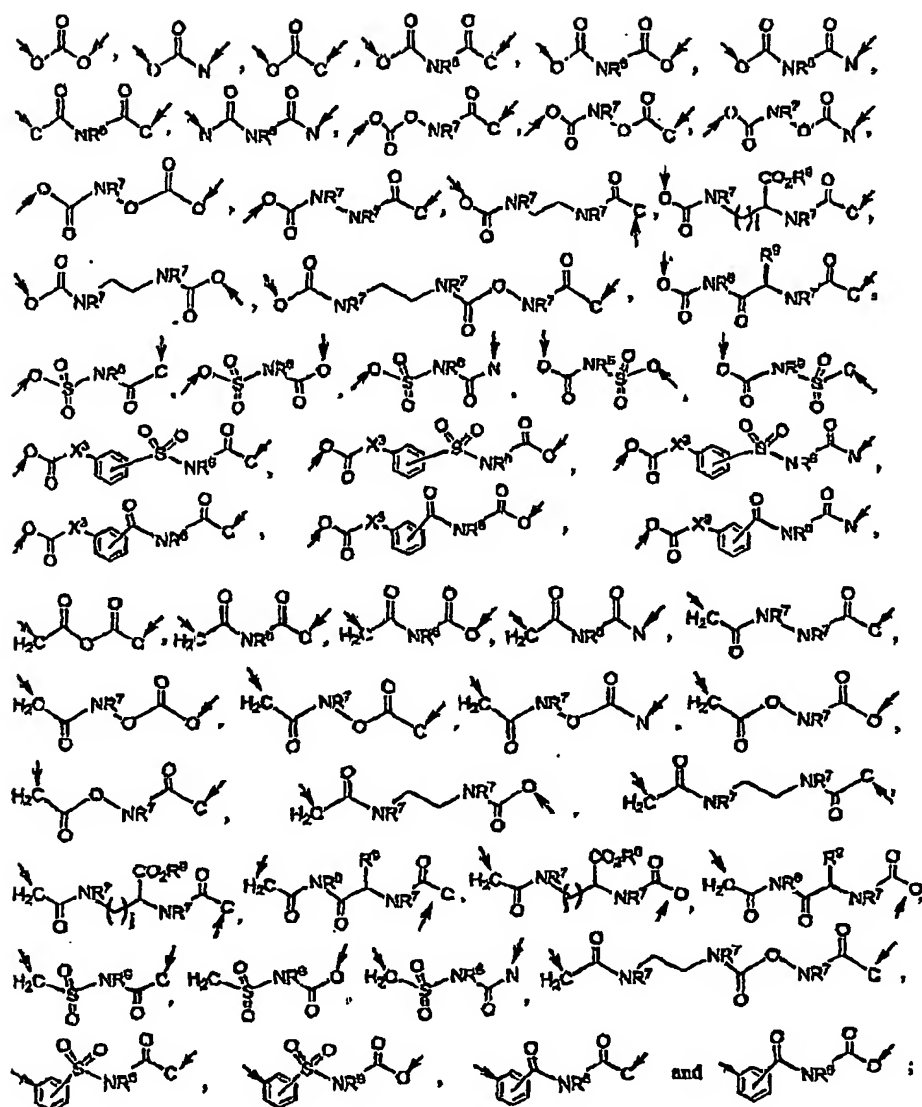
J is 1-4;

R¹⁰ and Rⁿ independently represent H, (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, or a group selected from the group consisting of:



with a proviso that when R^{10} is selected from the above group, R^{11} represents H or $(C_1-C_8)\text{alkyl}$, and when R^{11} is selected from the above group, R^{10} represents H or $(C_1-C_8)\text{alkyl}$;

- 5 R^{12} independently represents a group selected from the group consisting of:



X^3 is independently O or NR^7 .

- 5 D^1 and D^2 of the present invention can be both known and investigational drugs compiled in drug databases such as the Merck Index, IDdb, Prous Science's Integrity[®],

Prous Science Drugs of the Future™, The Ensemble® and the like. In a double prodrug, D¹ and D² are the same drugs. In a mutual prodrug, D¹ and D² are different drugs. In some prodrugs, only D¹ is a drug and D² may not be a drug at all. Here -OH, -SH, >NH₂, -NHR¹, -C(=O)H, -CONHR¹, -OC(O)NHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹)C(=O)NBR* and -N(R¹)SO₂NHR¹ functional groups in D¹ and D² of formula I participate in the formation of linkages between the drug and the linker. Accordingly, some of the atoms or groups in L¹ and L² may come from the corresponding D¹, D² or linker.

Another embodiment of the invention is the compound of formula I, wherein D² is an amino-, carboxyl-, or hydroxyl-containing group or molecule comprising one or more water solubilizing functional groups selected from the group consisting of hydroxyl, amino, acylamino, carboxyl, sulphate, sulfonate, phosphate, phosphonate, N-acetylsulfonamide, N-acetylsulfamate, N-acylcarbamate, N-alkylcarbamate metallic salts, and amino acids to give water-soluble prodrug.

Another embodiment of the invention is the compound of formula I, wherein D² is selected from the group of D, L and DL amino acids consisting of Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.

Another embodiment of the invention is the compound of formula I, wherein P represents a polymer selected from the group consisting of albinogalactan, polyamino acids, polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyacrylic acid, poly(2-hydroxyethyl 1-glutamate), dextran and modified dextrans such as dextran aldehyde, carboxymethyl dextran, arabinogalactan aldehyde, carboxymethyl chitosan, and hyaluronic acid.

Yet another embodiment of the invention is the compound of formula I, wherein D² is a polypeptide selected from group consisting of poly(L-glutamic acid), poly(D-glutamic acid), poly(DL-glutamic acid), poly(L-aspartic acid), poly(D-aspartic acid), poly(DL-aspartic acid), copolymers of the polyamino acids and polyethylene glycol,

Another embodiment of the invention is the compound of formula I, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltons. Yet another

embodiment of the invention is the compound of formula %wherein, the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.

In a further embodiment D² is a peptide, protein or monoclonal antibody for achieving targeted delivery of prodrugs and drugs. Another embodiment of the invention is the compound of formula I, wherein D² is a ligand or dipeptide or a dipeptide ligand. In a further embodiment D² is a dipeptide ligand that is a substrate for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. In a further embodiment D² is a targetable small peptide, i.e., dipeptide, tripeptide, tetrapeptide, etc.

Another embodiment of the invention is the compound of formula I, wherein O^1 is a vitamin. Such vitamin-conjugated prodrugs are expected to be taken up by U* diseased cells via receptor-mediated endocytosis. In a further embodiment of the invention is a compound of formula I, wherein D^1 is selected from the group of vitamins consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxin, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5-

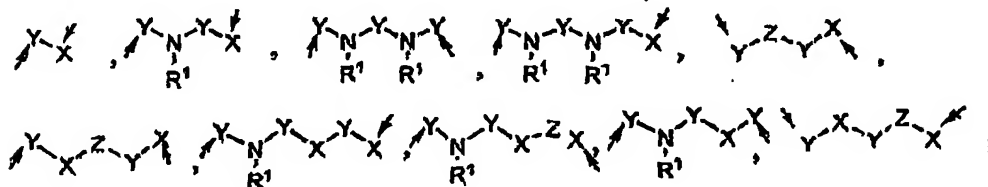
AnoHier embodiment of the invention is the compound of formula I, wherein D¹ and D² represent the same therapeutic agent to give a symmetrical double prodrug. Another embodiment of the invention is the compound of formula I, wherein D¹ and D² represent different therapeutic agents to give an unsymmetrical prodrug. Another embodiment of the invention is the compound of formula (I), wherein D¹ and D² can be cited from same or different therapeutic class. Another embodiment of the invention is the compound of formula (I)₄ wherein D¹ and D² can be same or different therapeutic agents, the four therapeutic agents may have same or different mechanisms of action or they may work on different biological targets or they may work on different disease conditions.

Another embodiment of the invention is the compound of formula I, where D^2 is R^2 , R^3 or R^4 . Another embodiment of the invention is the compound of formula I, wherein a is 0, B is $S-S$, $S \gg S=O$, $S-SO_a$ or $S-S=NH$. Yet another embodiment of the invention is the compound of formula I, wherein a is 0, B is $S-S$ or $S-S=O$, $S-SO_n$ $m \dot{a} D^2$ is R^2 or R^3 or R^4 . A further embodiment of the invention is the compound of formula I, wherein B is $S-S_A$ and A^1 are CH_2 , CH_2 , E is a bond and D^2 is R^a , R^3 or R^4 .

Another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S-O, S-SO₂; A and A¹ are CH₂-CH₂, E is a bond and D¹ is R⁴. Another embodiment of the invention, is the compound of formula I, wherein a is 0; B is S-S; A and A¹ are CH₂-CH₂, E is a bond and D¹ is R⁴.

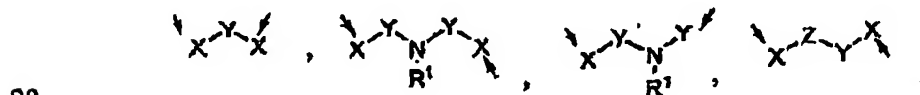
5 Another embodiment of the invention is the compound of formula I, wherein a is 0, B is a bond, (CHaX or (CHiCH₂O)₀; wherein b and c are as defined above. Another embodiment of the invention is the compound of formula I, wherein a is 0, B is a bond, (Cfi)b or (CHJCHJO)C and D² is R² or R³ or R⁴; wherein b and c are as defined above.

10 Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-SO₂; D¹ and D² are drug molecule of R² or R⁴ containing carboxyl group; L¹ and L² are independently selected from the following linkages;



wherein, X, R¹, Z are as defined above; and Y is C=O. In another embodiment, A and A¹ are CBfe-CKfe, and E is a bond. In a further embodiment, A and A¹ are 1,2-phenylene or 3-phenylene or 4-phenylene, and E is CHa.

15 Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-S-O, S-SO₂; D¹ and D² are drug molecule of R² or R⁴ containing amino- or hydroxy group, L¹ and L² are independently selected from the following linkages:



20 wherein, X, R¹, Z are as defined; and T is CK). In another embodiment, A and A¹ are CHb-CH₂, and E is a bond. In a further embodiment, A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene, and E is CHz.

25 Yet another embodiment of the invention is the compound of formula I, wherein a is 0; B is S-S or S-SO₂; D¹ and D² are drug molecule of R² or R⁴ containing amino- or hydroxy group, L¹ and L² are independently selected from the following linkages:

CH₂, E is a bond and D² is D¹. Another embodiment of the invention is the compound of formula I₉ wherein a is O; B is S-S or S-S=O, S-SO₂; A and A¹ are 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and D² is P¹ or R² or R³ or R⁴. Another embodiment of the invention is the compound of formula I, wherein a is O; B is S-S; A and A¹ are 1-phenylene, 1,3-phenylene or 1,4-phenylene; E is CH₂ and P² is P¹ or R² or R³ or R⁴. A further embodiment of the invention is the compound of formula I, wherein B is S-S, A and A¹ are CH₂-CH₂, E is a bond and P² is a dipeptide ligand.

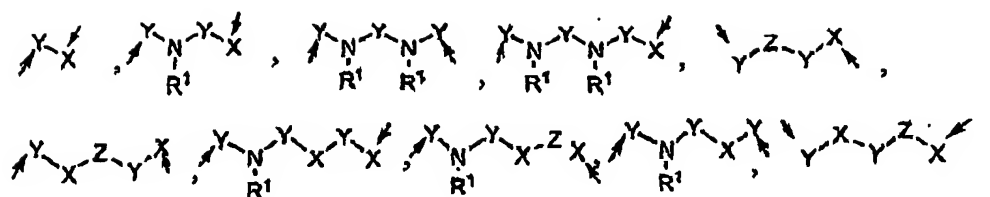
Yet another embodiment of the invention is the compound of formula I, wherein a is O; B is S-S or S-S=O, S-SO₂; A and A¹ are CH₂-CH₂, E is a bond and P² is a dipeptide ligand. The peptide ligands used in the invention can be substrates for intestinal transporters for selective intestinal absorption of the corresponding prodrugs thereby increasing the bioavailability of the prodrugs. An embodiment of the present invention is the compounds of formula (I), wherein D¹, L¹ and L² are aa defined above; A and A¹ are CH₂; E is a bond; B is a bond or (CH₂)_b; b is 1-6; a is O; and D³ is D¹ or R² or R⁴.

Another embodiment of the present invention is the compound of formula (I), wherein E, D* and V are as defined; L³ is O; A and A¹ are independently (CH₂)_d, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; d is 1-4; B is S-S, S-S=O, S-SO₂ or S-S=NH; a is O; D² is NO, NO₂ or a nitric oxide releasing molecule such as KONOate. In a further embodiment, P² is a IONOate selected from the group consisting of:



one of the above; B is S-S.

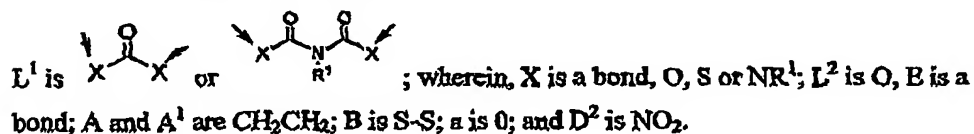
Another embodiment of the present invention is the compound of formula (I), L² is O; A and A¹ are independently (CH₂)_{dj}, 1,2-phenylene, 1,3-phenylene or 1,4-phenylene; d is 1-4; B is S-S; a is O; P² is NO₂. In a further embodiment, when A and A¹ are CH₂-CH₂, E is a bond, yet another embodiment, when E is CH₂, A and A¹ are independently 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene.



wherein, X is independently a bond, O or NR¹, R¹ is not a bond; Y is C=O or SO₂; A and A¹ are CH₂CH₂; B is S-S; a is O and D² is NO₂.

- Another embodiment of the present invention is the compounds of formula (I),
- 5 wherein D¹ is an antioxidant or free radical scavenger such as a hydroxyl-containing stable radical such as 2,2,6,6-tetramethylpiperidin-1-oxyl (4-hydroxy-TEMPO), 4-cyanophenyl-2,2,6,6-tetramethylpiperidin-1-ol (4-cyanophenyl-TEMPO) or any other known hydroxyl-containing antioxidants or radical/superoxide scavengers and D² is NO₂. The amino-oxyl/hydroxyl-containing antioxidants and
- 10 radical/superoxide scavengers can be known, not investigational.

An embodiment of the present invention is the compound of formula (I), wherein



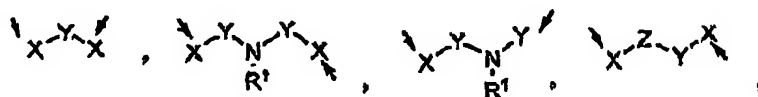
L¹ is $\text{X}-\text{Y}-\text{X}$ or $\text{X}-\text{N}(\text{R}^1)-\text{Y}-\text{X}$; wherein, X is a bond, O, S or NR¹; L² is O, B is a bond; A and A¹ are CH₂CH₂; B is S-S; a is O; and D² is NO₂.

- An embodiment of the present invention is the compounds of formula ϕ , wherein
- 15 V* and L* are as defined above; L* is O; A is 1,2-phenylene, 1,3-phenylene, or 1,4-phenylene; A* is CH₂ and E is CH₂; B is S-S; a is O and D² is NO₂.

An embodiment of the present invention is the compounds of formula Q, wherein

β is O; A and A¹ are CH₂; E is CH₂; B is a bond or (CH₂)_n; n is 1-6; a is O; D² is NO₂ and L¹ is a group selected from,

20



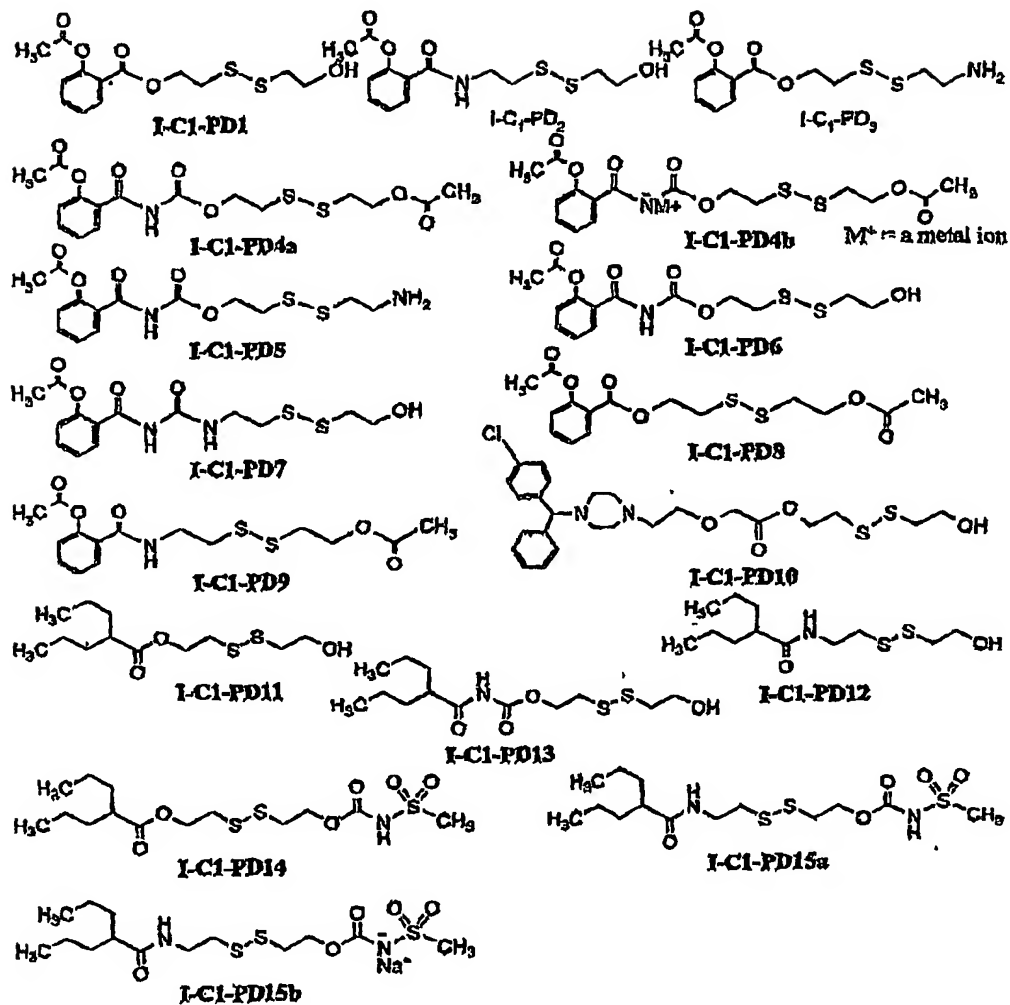
wherein, X is O, S or NR¹; R¹ is as defined.

An embodiment of the invention is the compound of formula I selected from the groups consisting of:

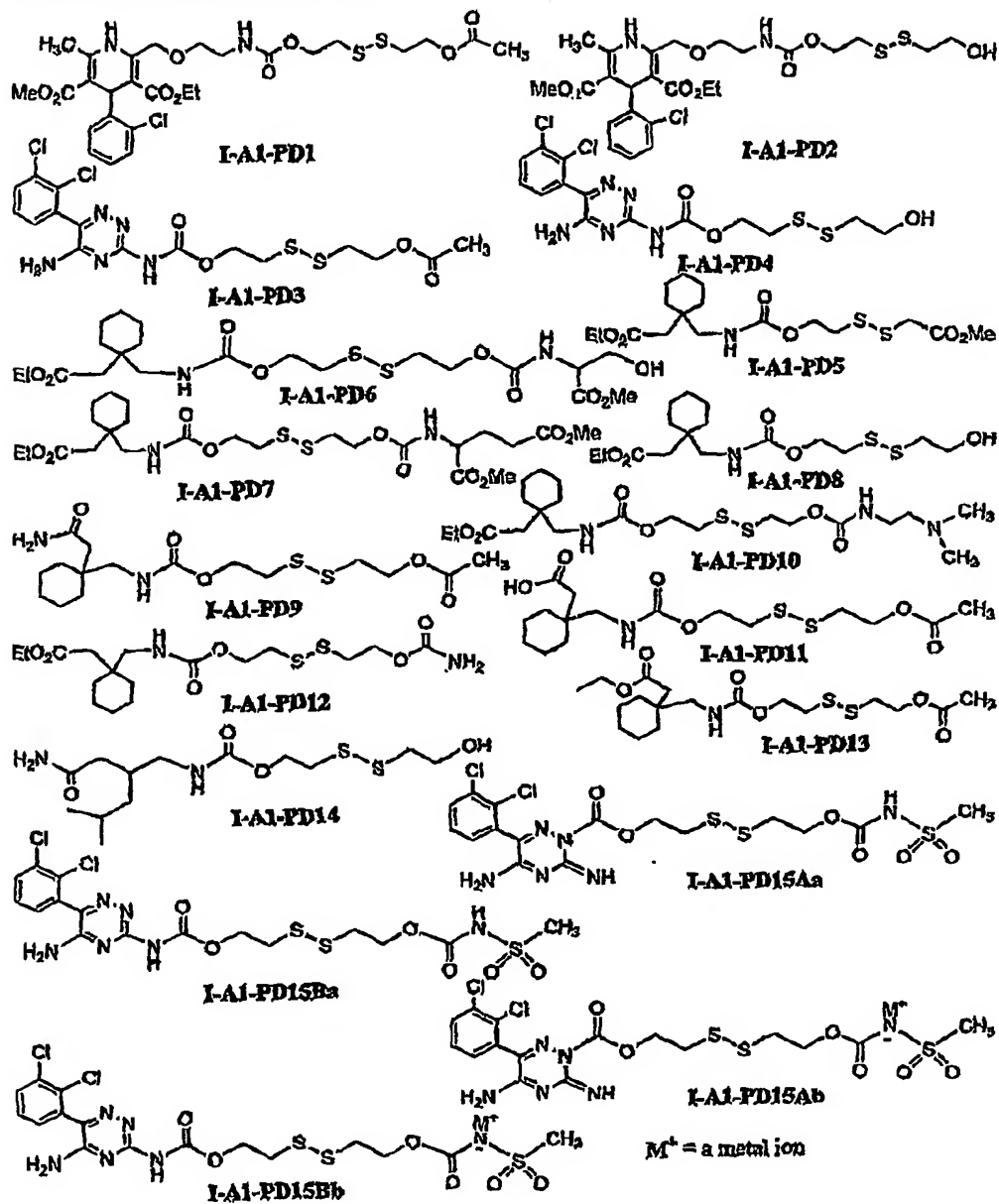
A. Prodrugs:

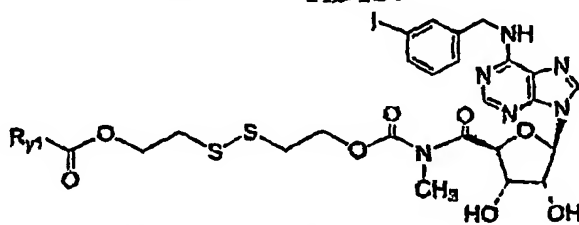
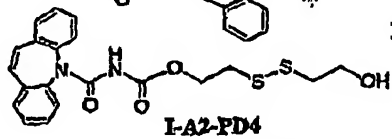
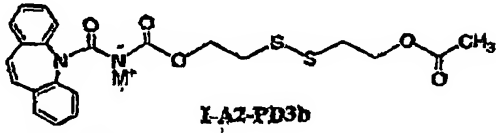
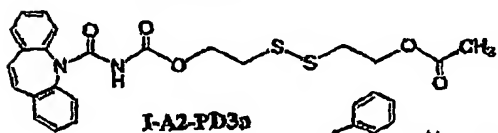
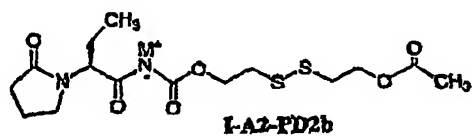
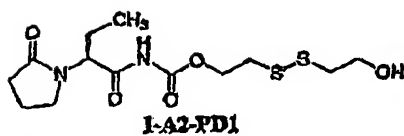
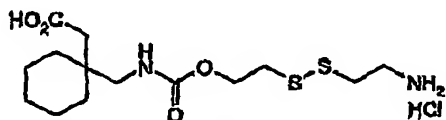
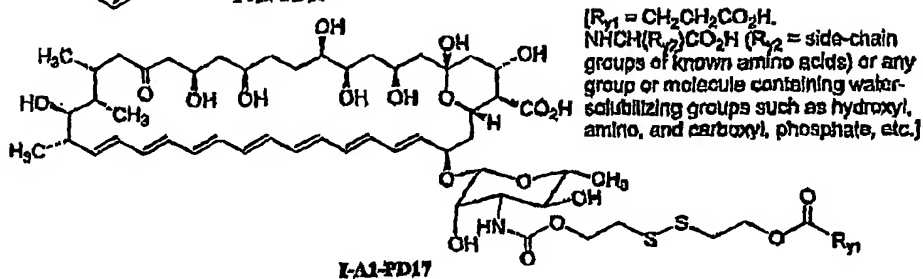
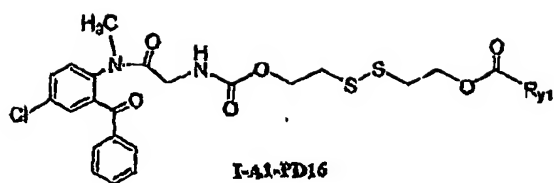
(a) From carboxyl-containing drugs:

3



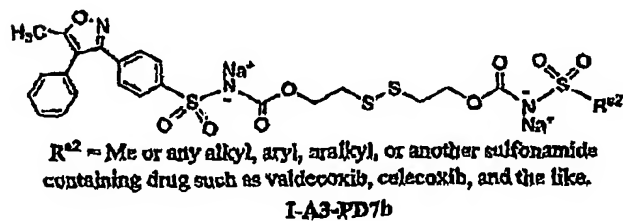
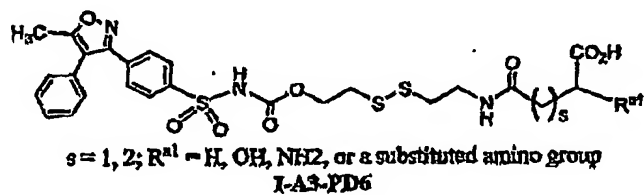
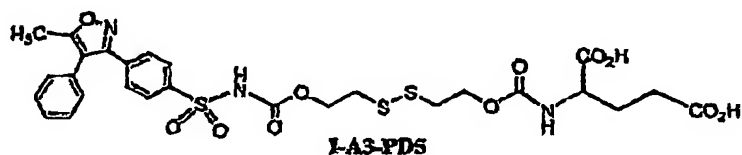
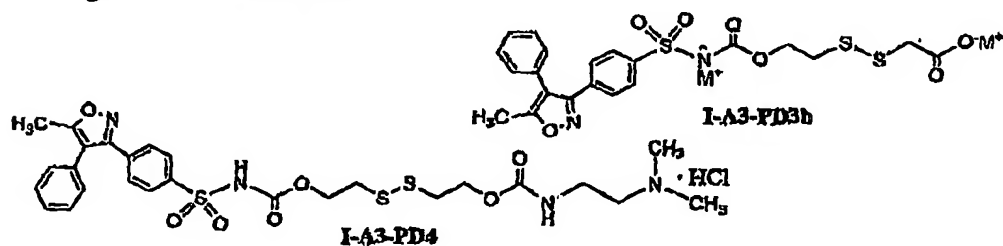
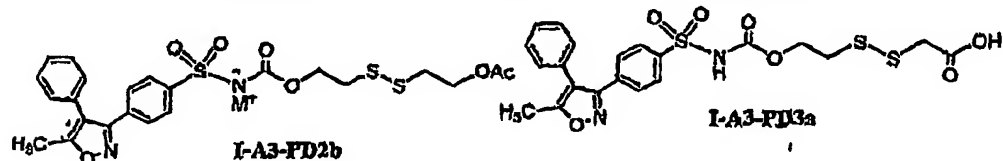
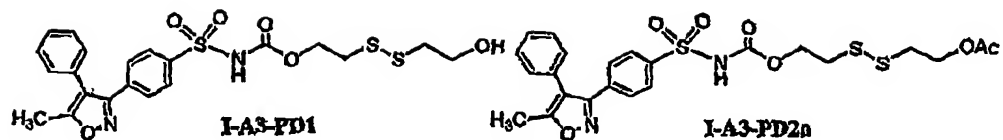
(b) From amino-containing drugs:



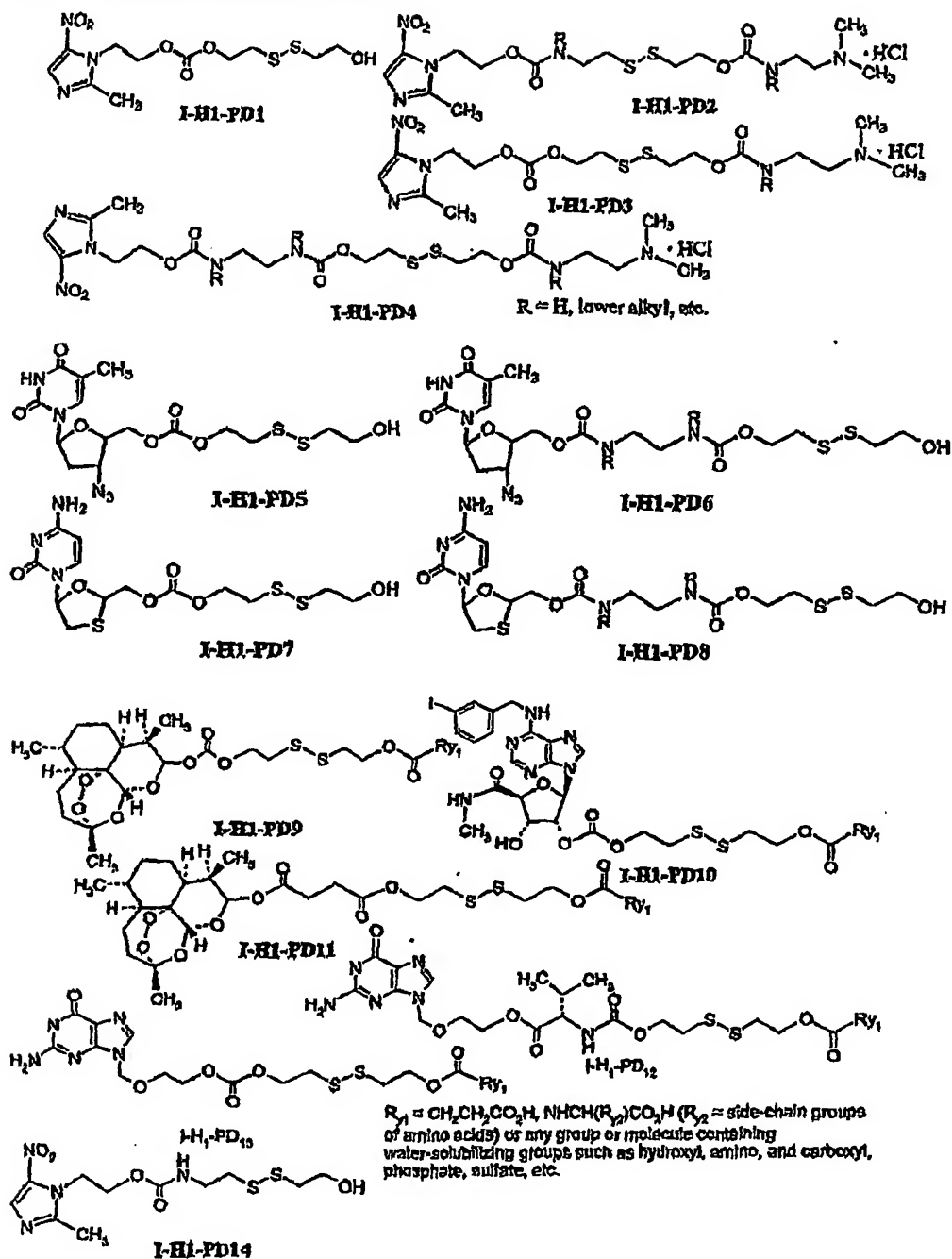


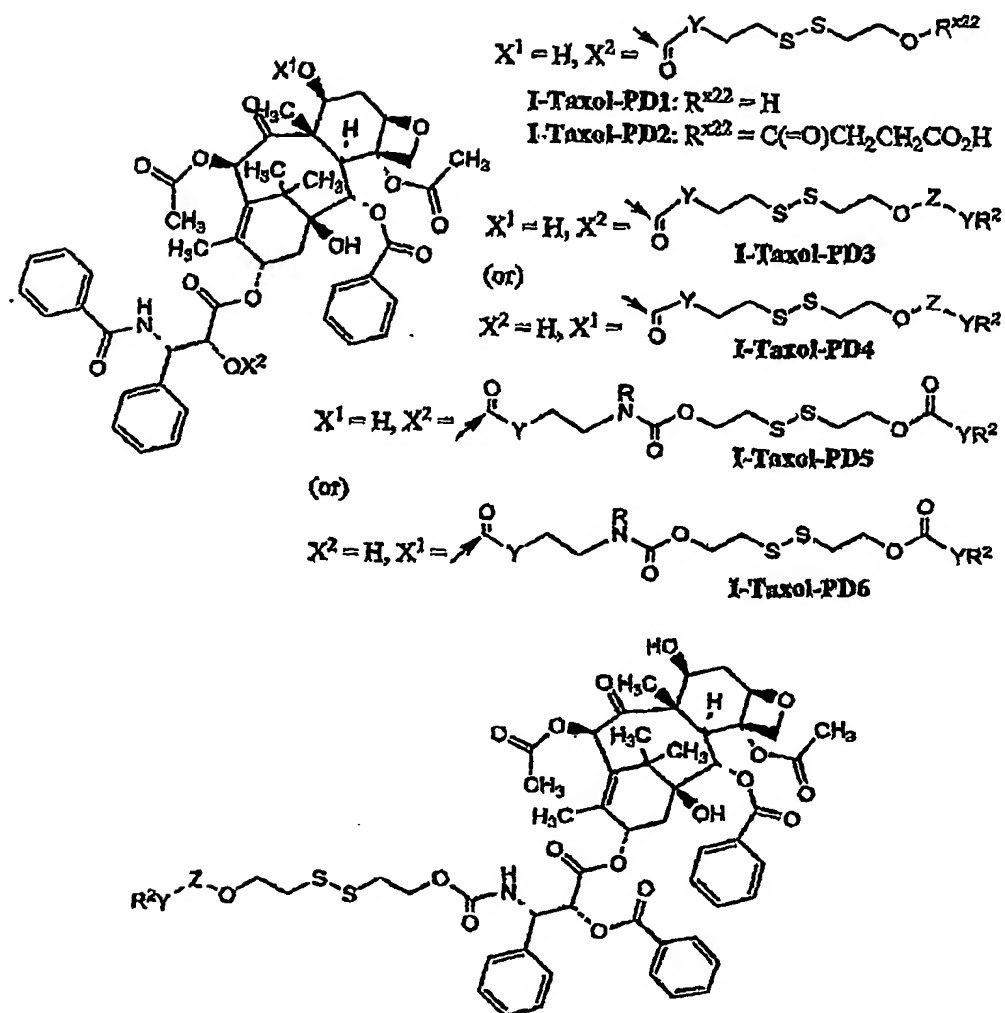
R_{y1} = An amino-, hydroxyl-containing molecule with water-solubilizing groups

I-A2-PD5



(c) From hydroxyl-containing drugs:





A PRODRUG OF ISOTAXEL

I-S23-PD1

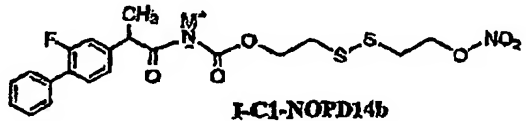
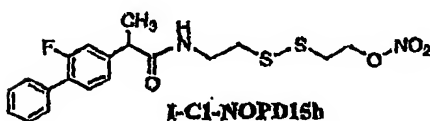
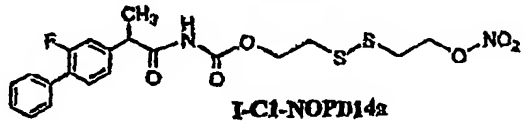
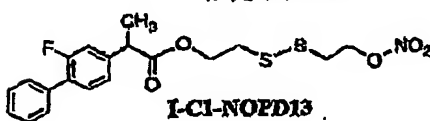
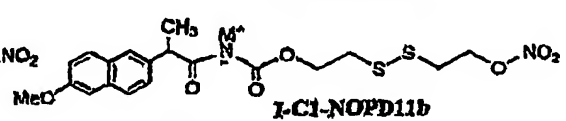
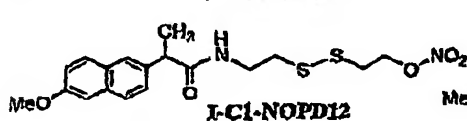
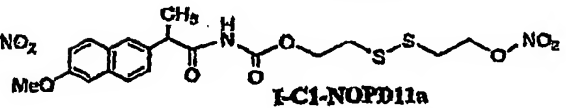
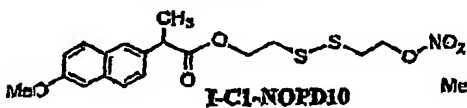
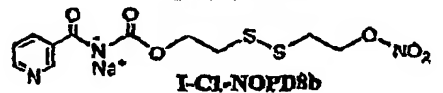
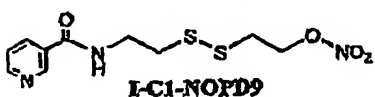
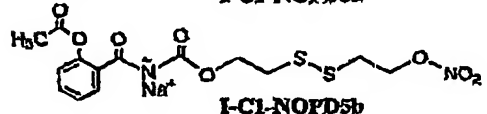
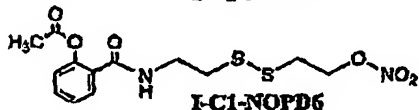
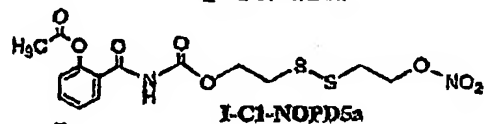
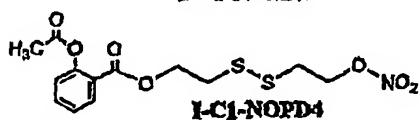
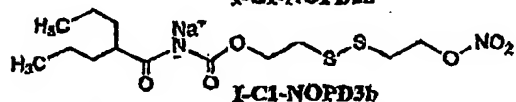
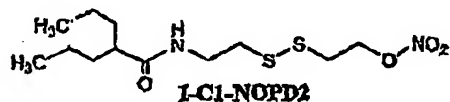
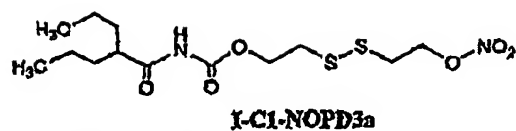
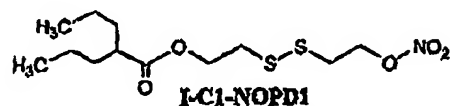
$\text{Y} = \text{O}, \text{NR}^1$ ($\text{R}^1 = \text{H}, \text{Alkyl}, \text{Aralkyl}, \text{Cycloalkyl}, (\text{CH}_2)_n\text{C}(=\text{O})$ ($n=1-6$), $(\text{CH}_2)_n\text{CO}_2^-$)

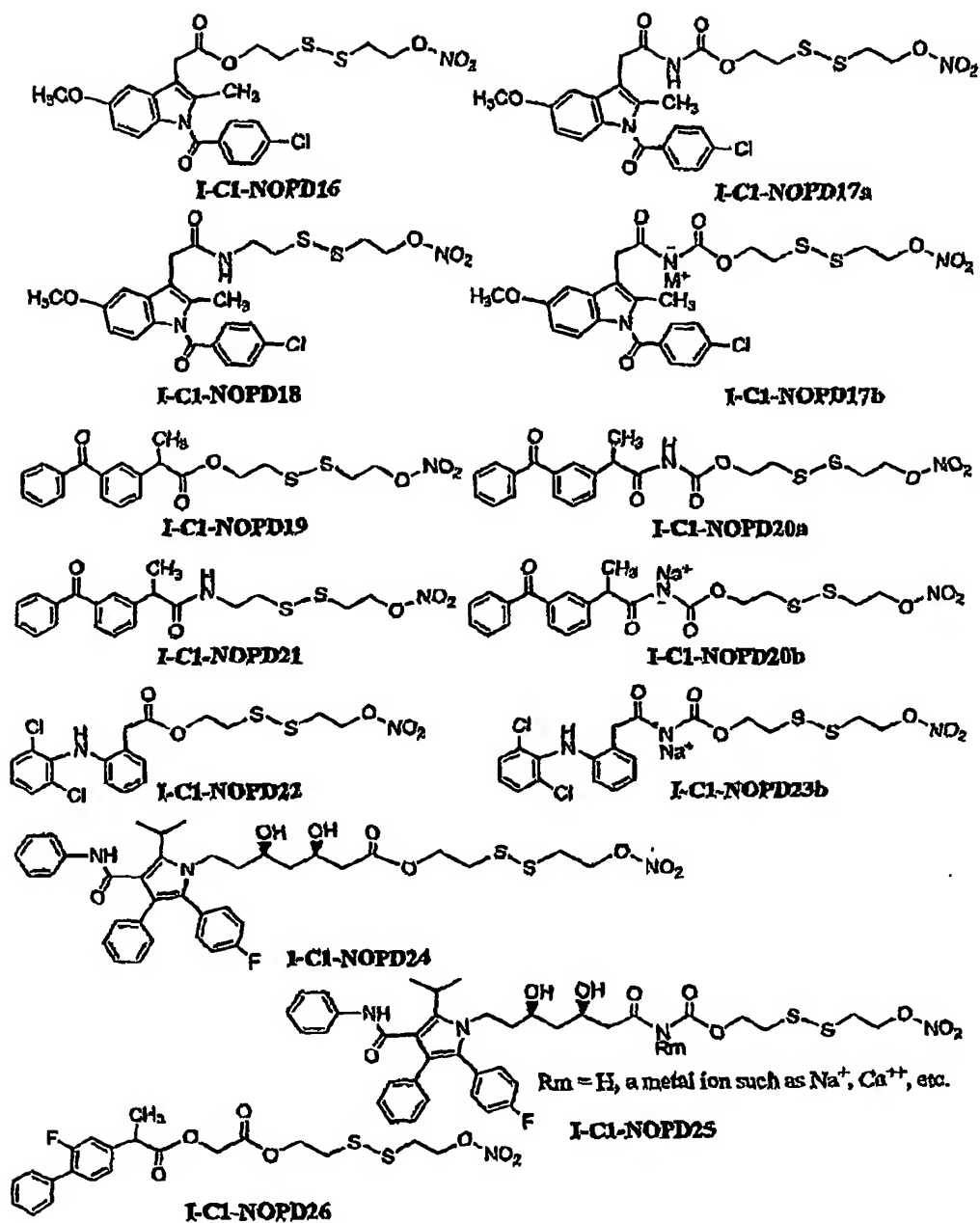
$\text{Z} = \text{C}=\text{O}, \text{SO}_2, \text{P}(=\text{O})\text{YR}^3$ ($\text{R}^3 = \text{H}$ or a metal ion)

$\text{R}^2 = \text{H}, \text{a bond}, \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2, \text{HCl}, \text{an Amino acid}, \text{or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such as } \text{Na}^+, \text{Ca}^{2+}, \text{etc.}$

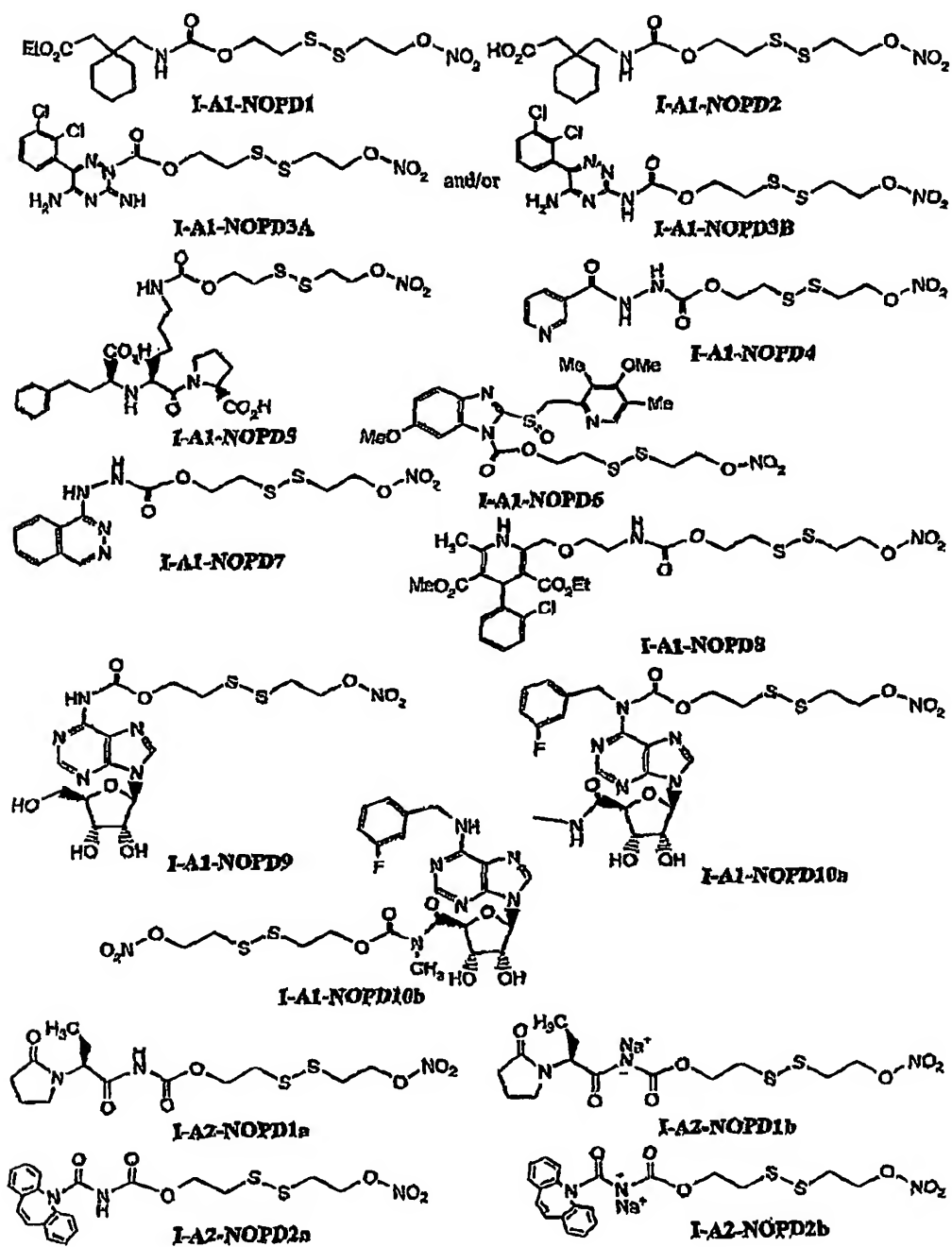
B. NO-releasing Prodrugs

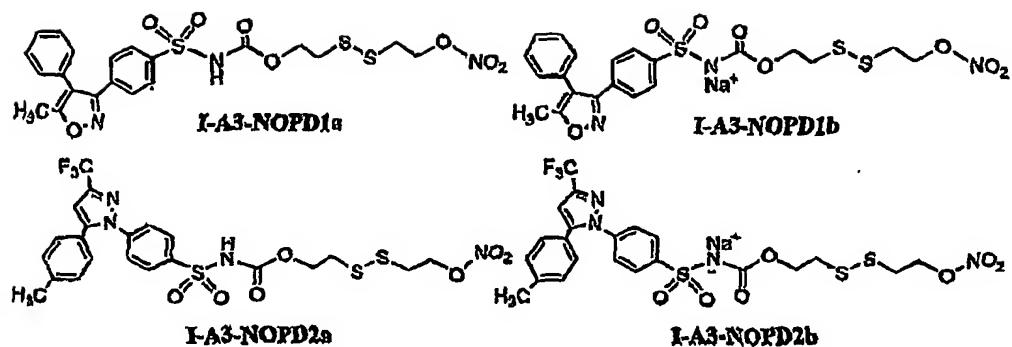
(a) From carboxyl-containing drugs



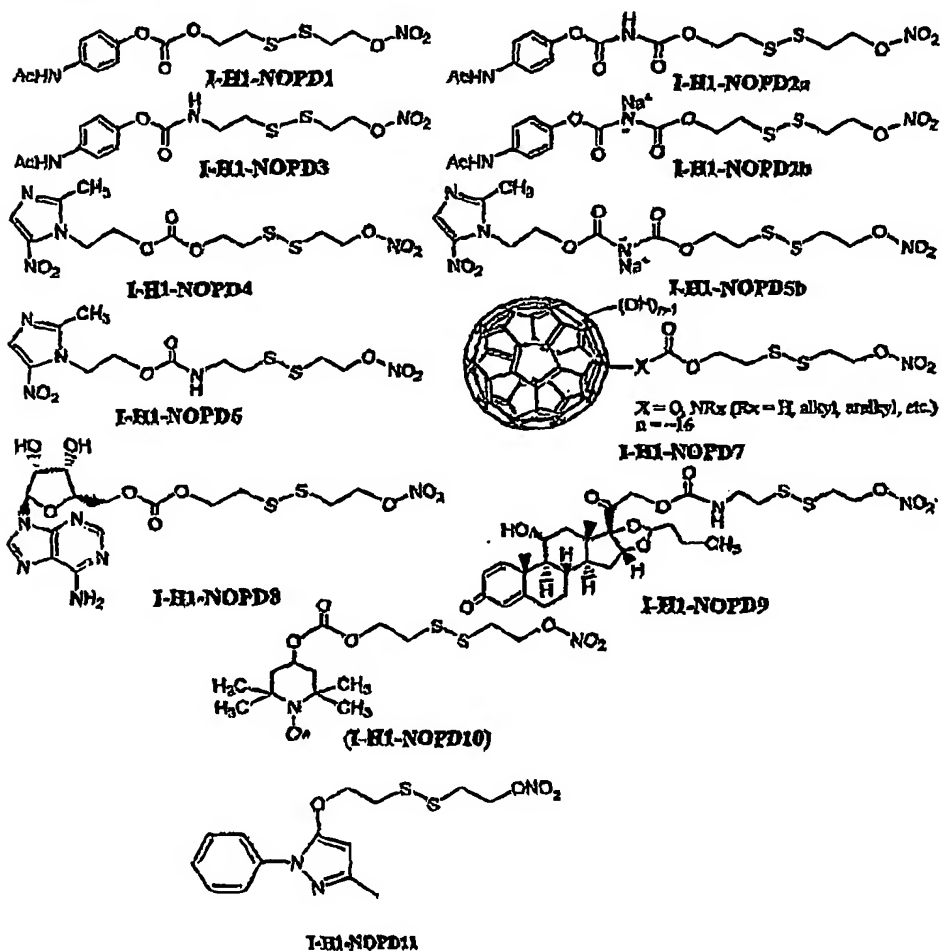


(b) From amino-containing drugs

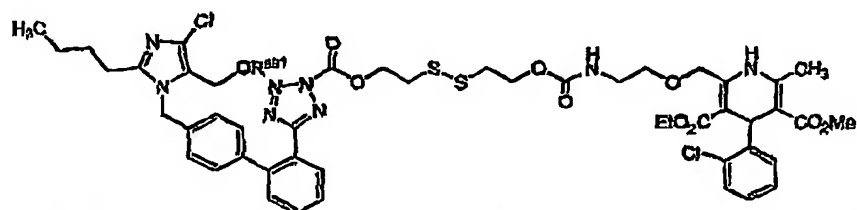
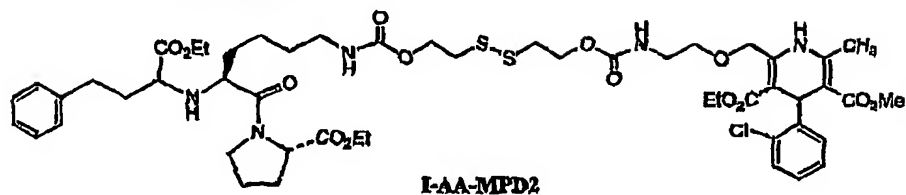
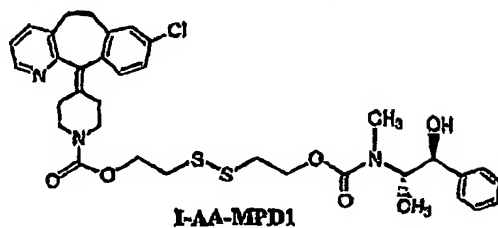




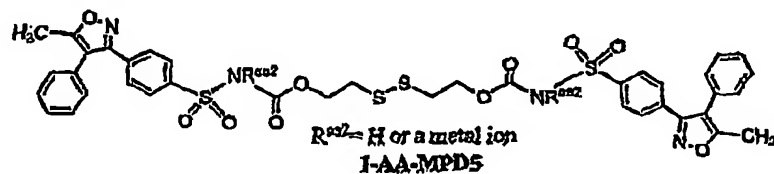
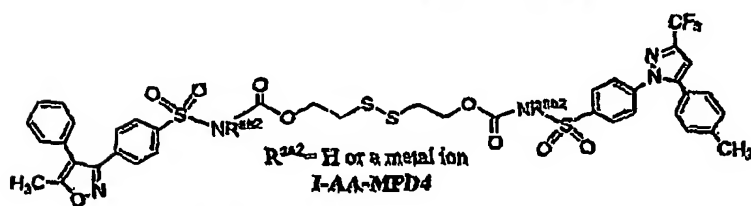
(c) From hydroxyl-containing drugs

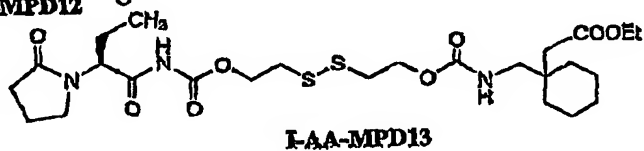
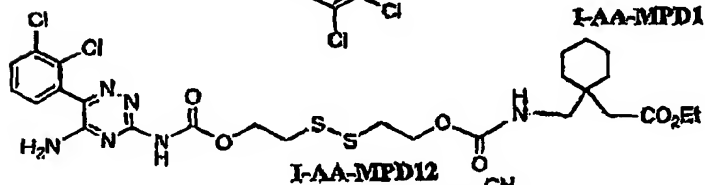
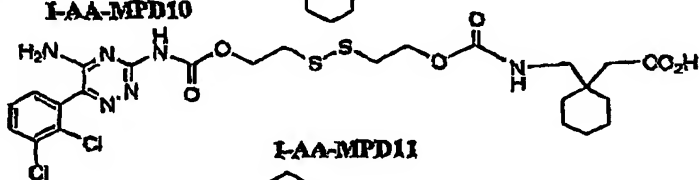
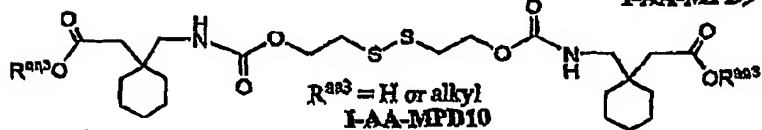
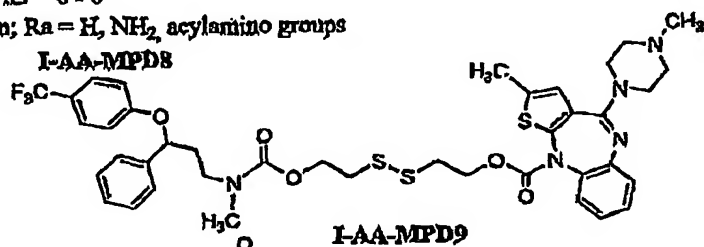
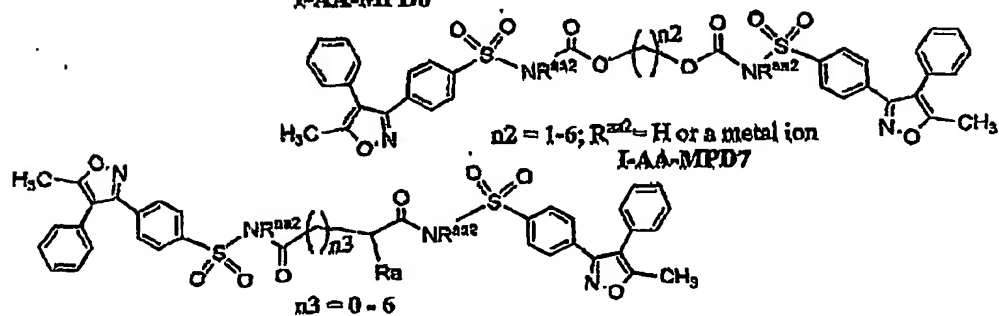
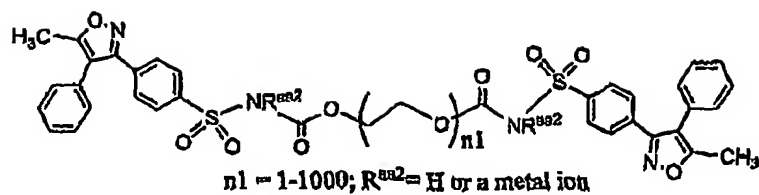


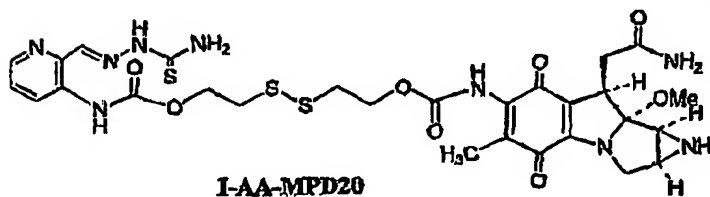
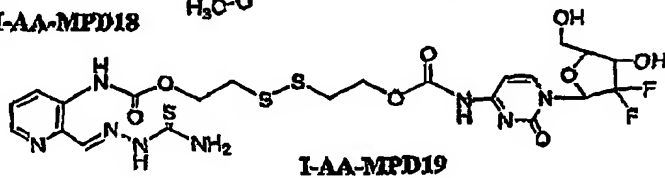
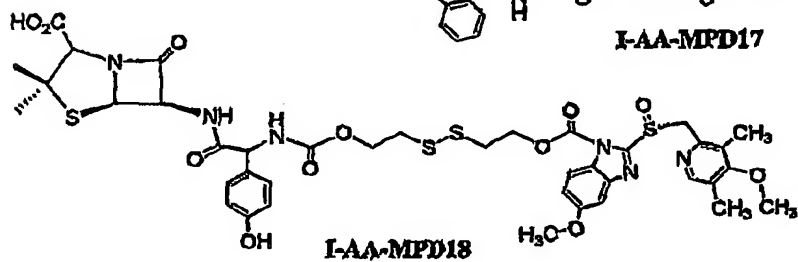
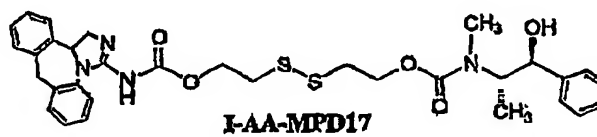
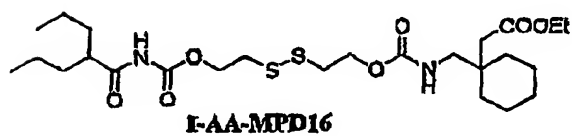
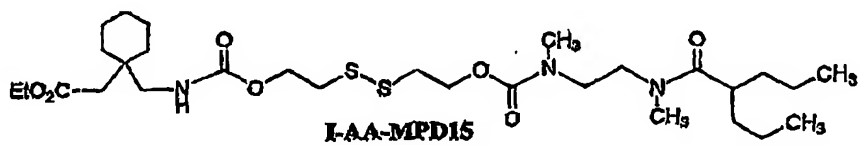
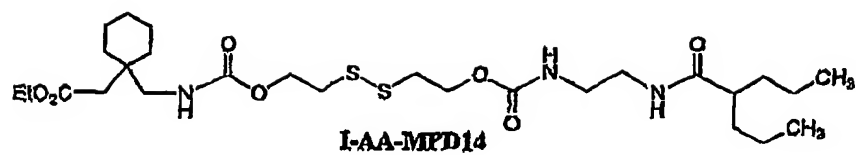
C. Mutual or Double Prodrugs
 (a) From two amino-containing drugs

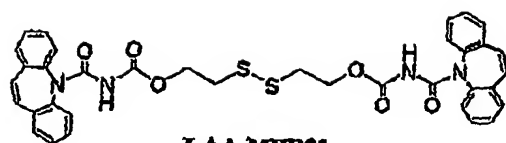
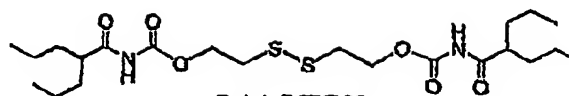
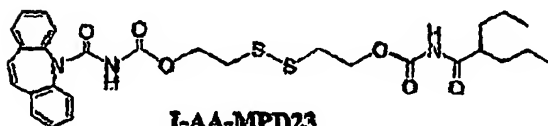
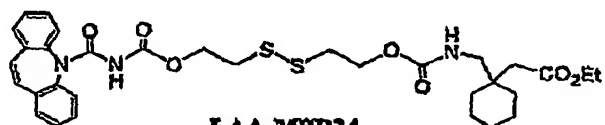
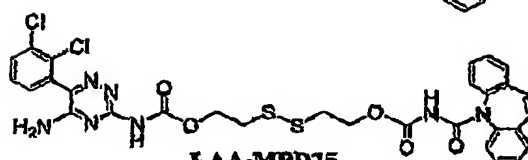
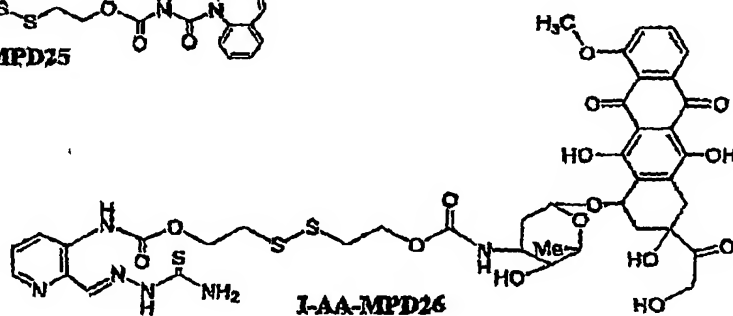
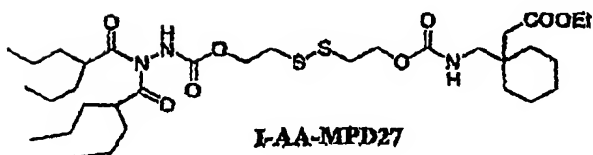


$R^{aa1} = H, PO_3H_2, C(O)NHCH_2CH_2NMe_2, C(O)CH_2NR^2$ ($R^2 = H$ or Alkyl),
 $C(O)OCH_2CH_2NMe_2, C(O)CH_2CH_2CO_2H, C(O)NHCH_2CH_2NHCOCH_2CH_2CO_2H,$
 $C(O)O(CH_2)_2NHCO(CH_2)_2CO_2H,$ and $C(O)CH_2N(CH_2CO_2H)_2.$

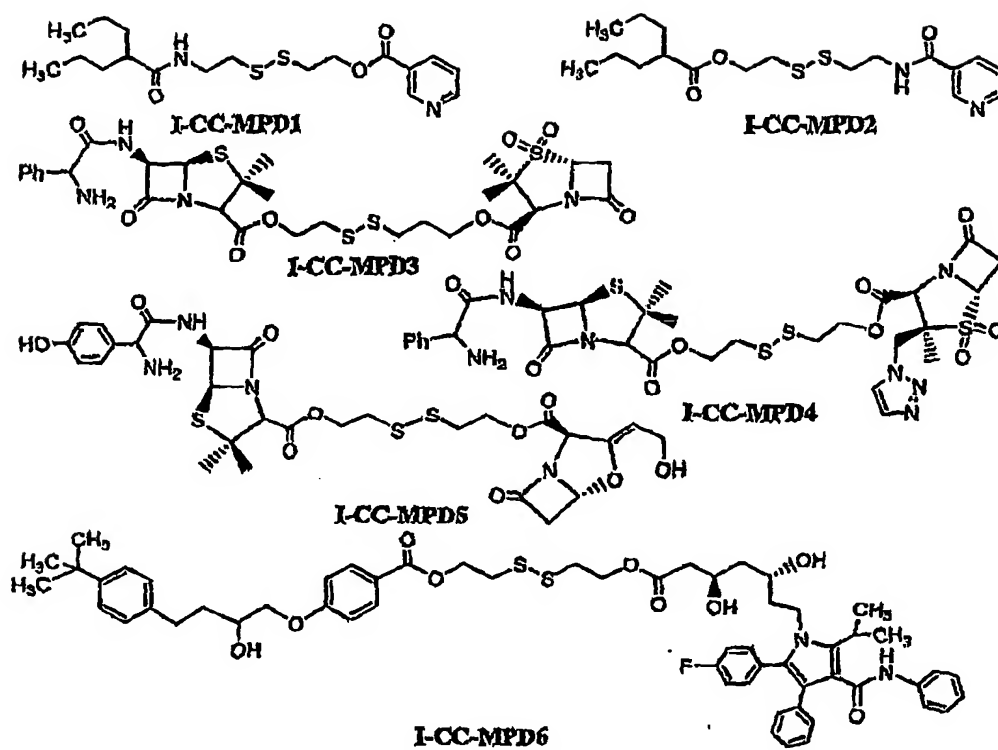




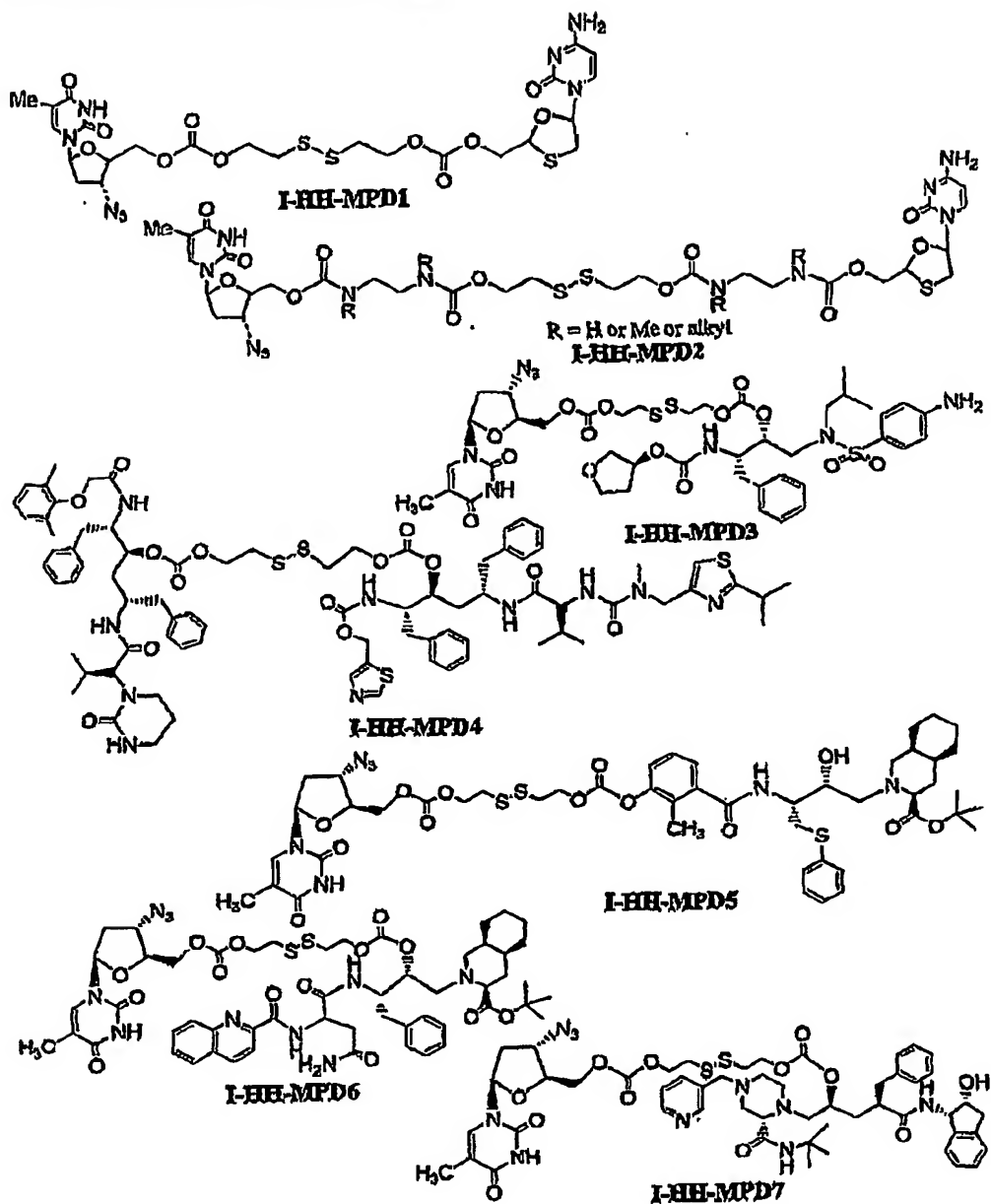


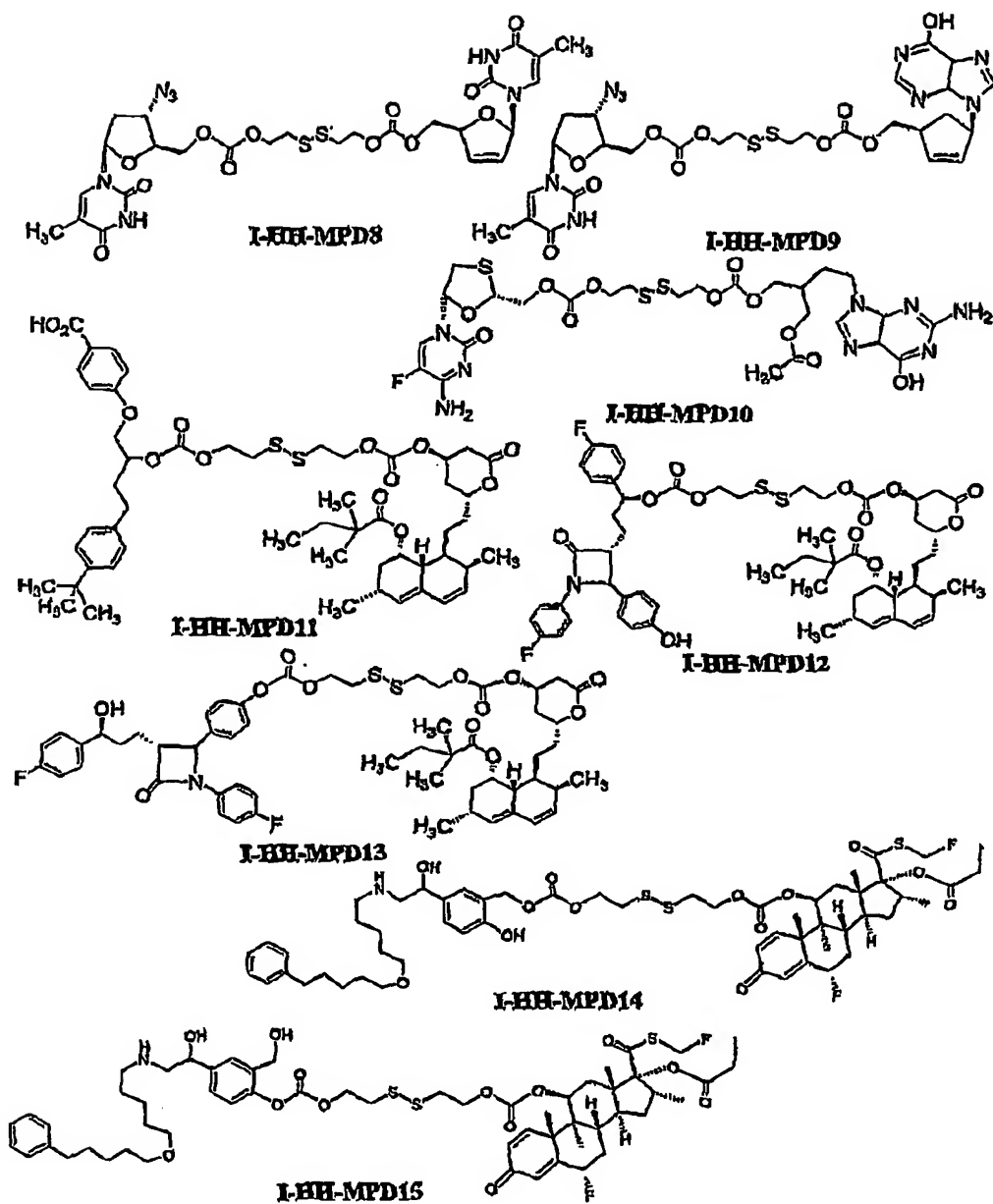
**I-AA-MPD21****I-AA-MPD22****I-AA-MPD23****I-AA-MPD24****I-AA-MPD25****I-AA-MPD26****I-AA-MPD27**

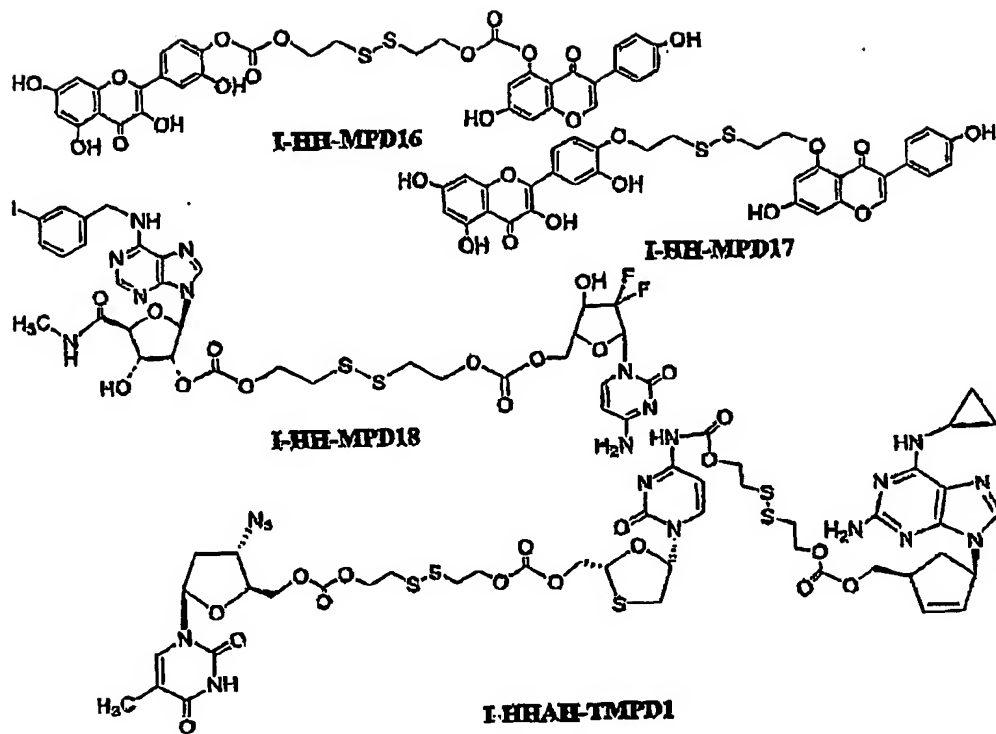
(b) From two carboxyl-containing drugs



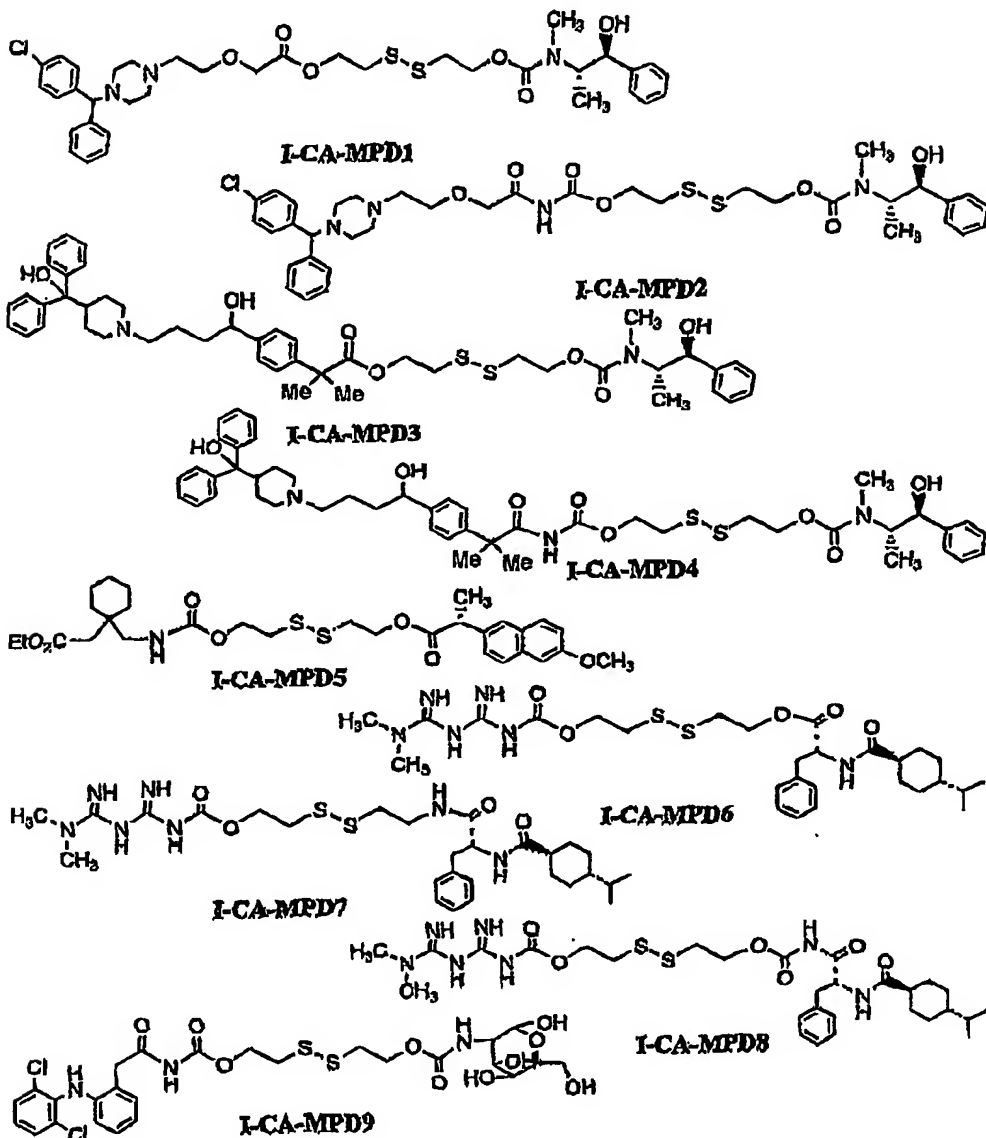
(c) From two hydroxyl-containing drugs

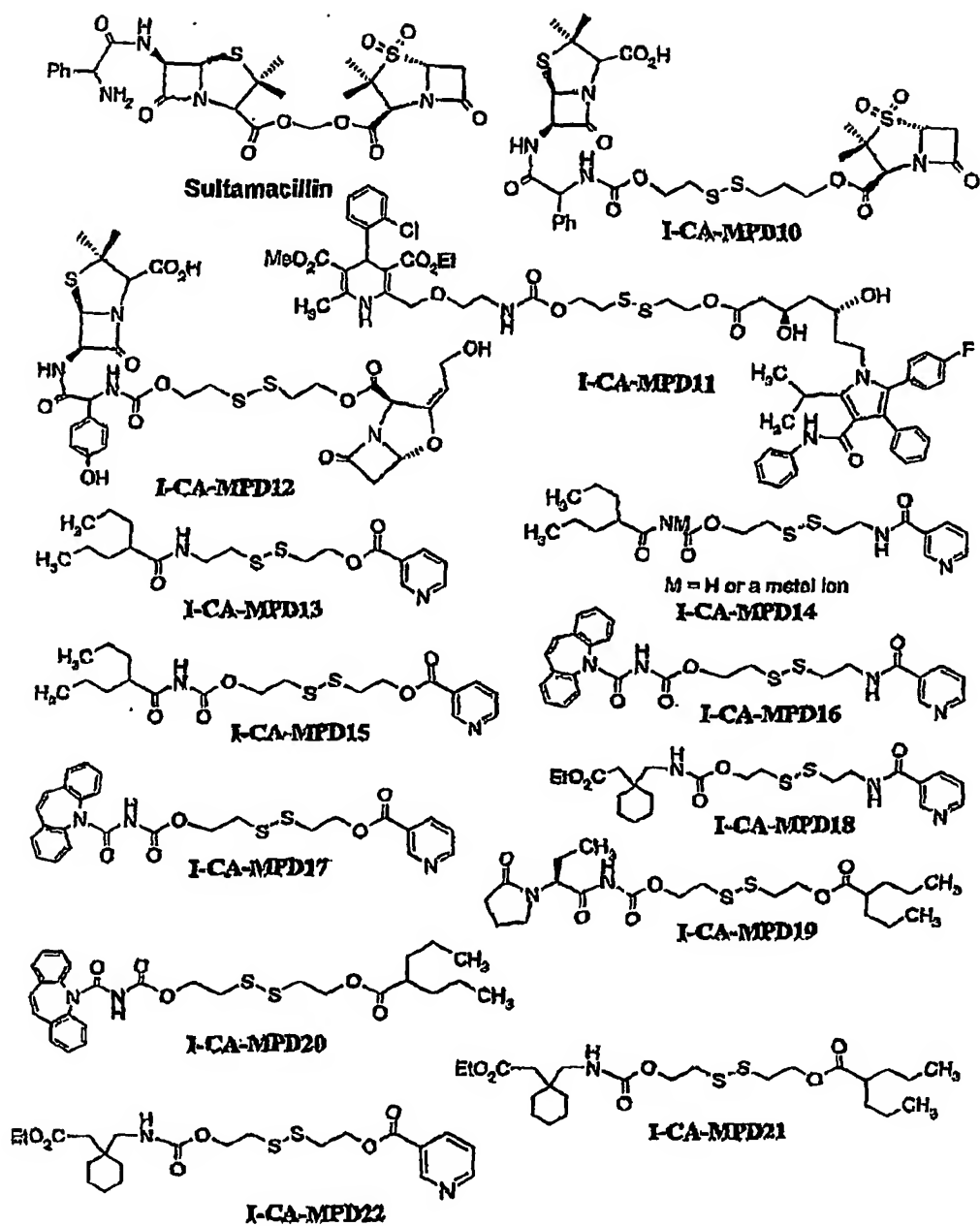


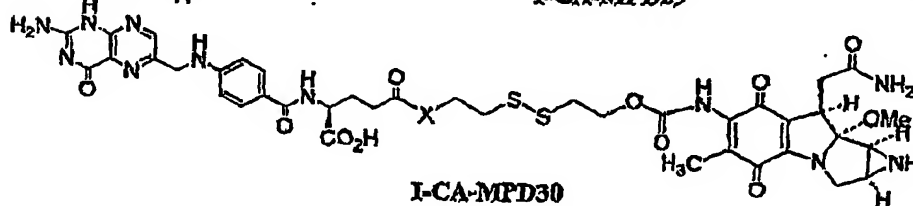
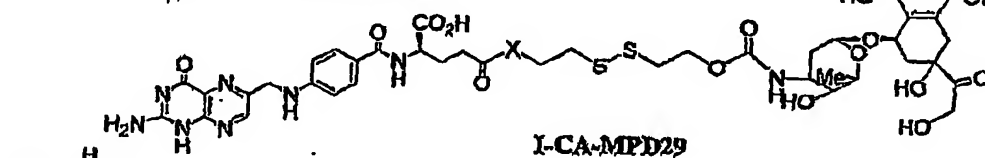
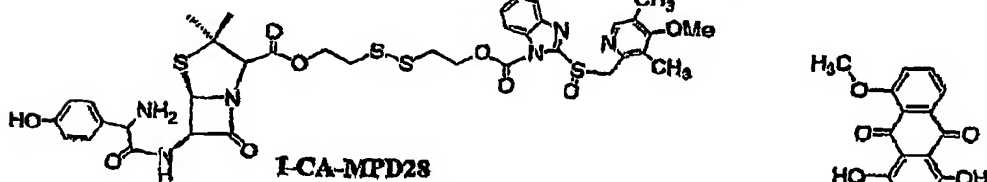
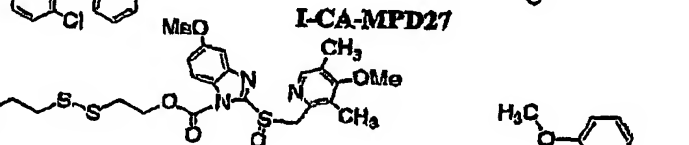
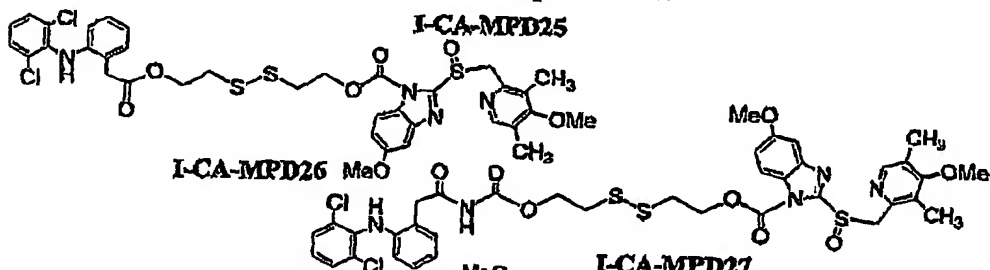
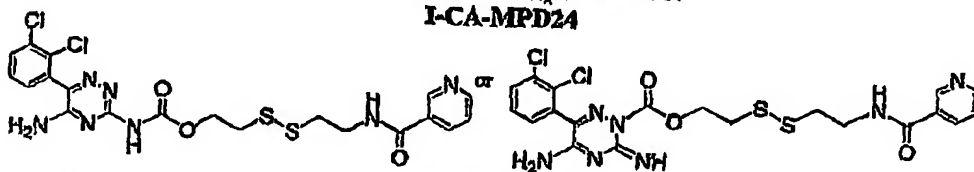
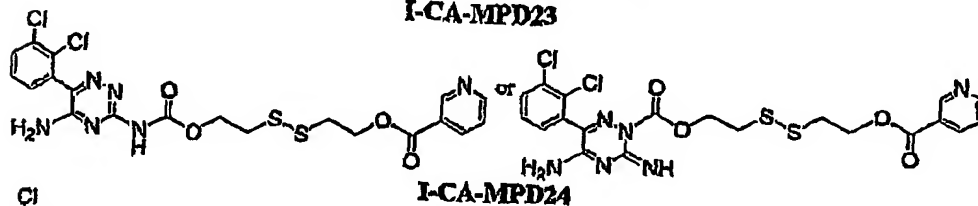
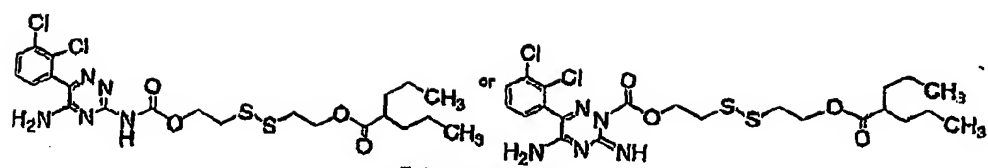




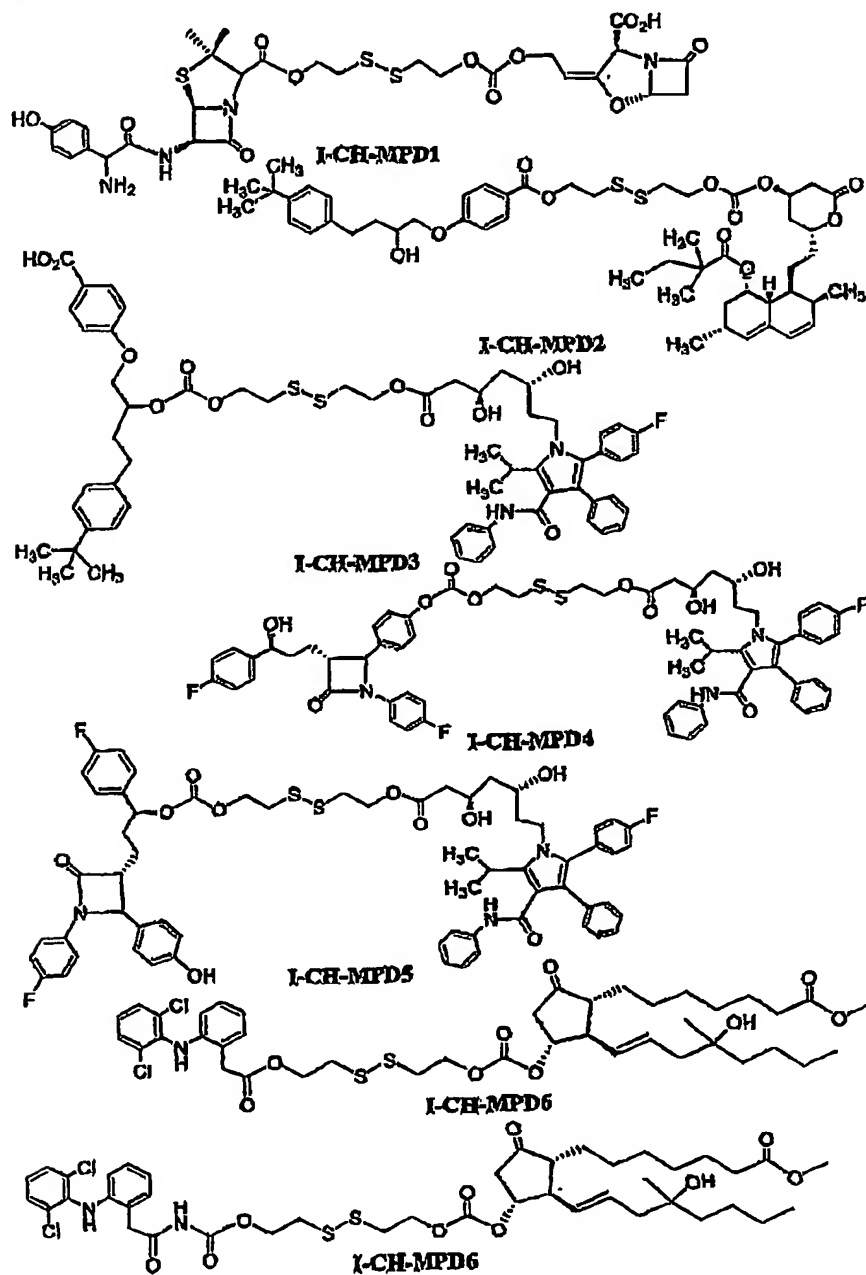
(d) From an amino-containing drug and a carboxyl-containing drug:



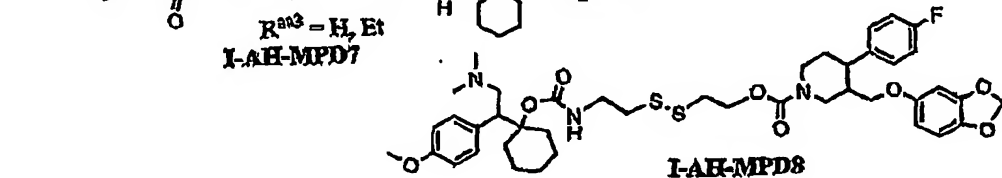
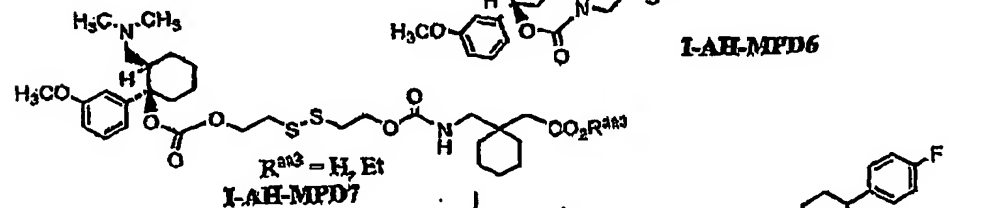
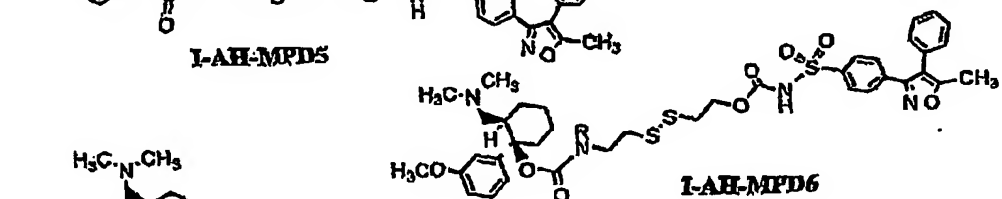
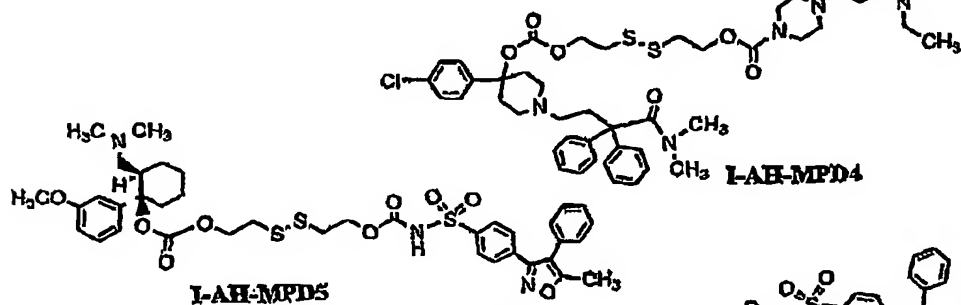
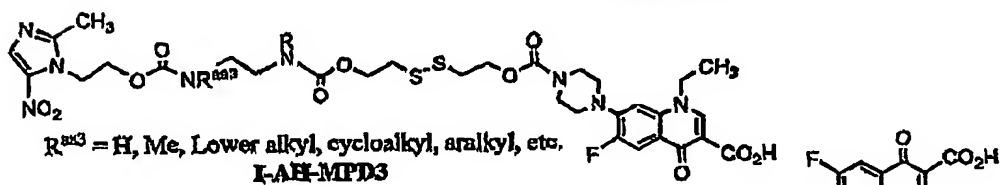
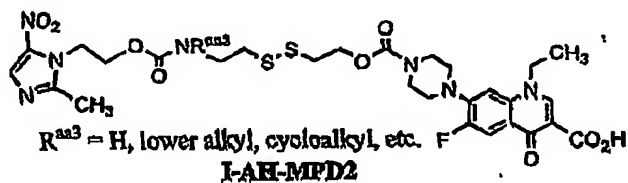
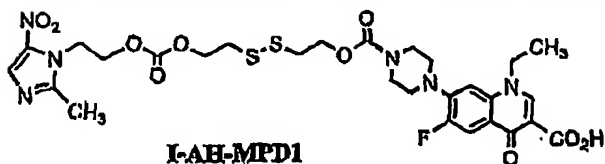


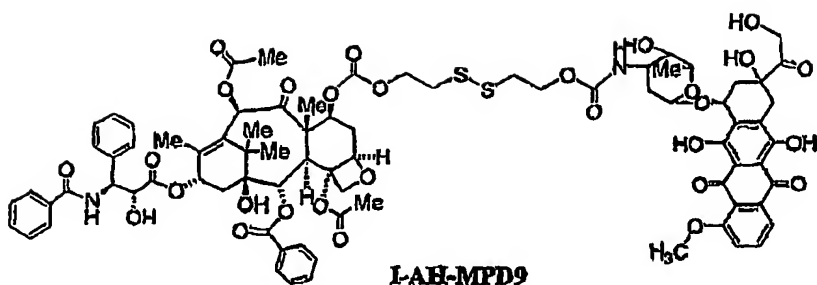
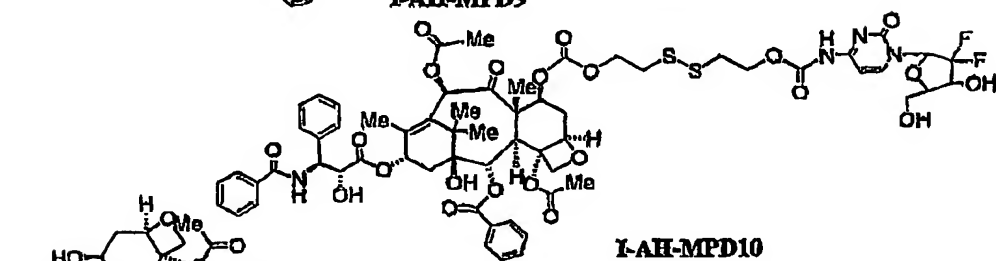
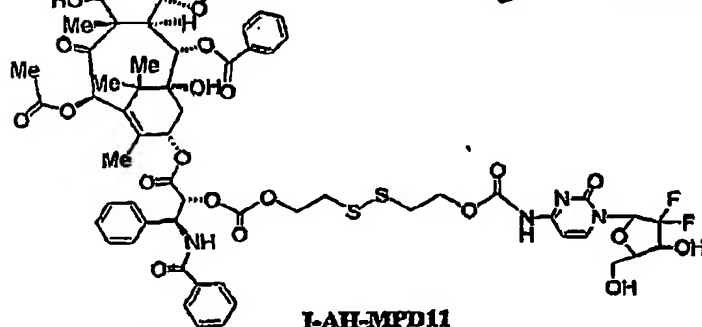
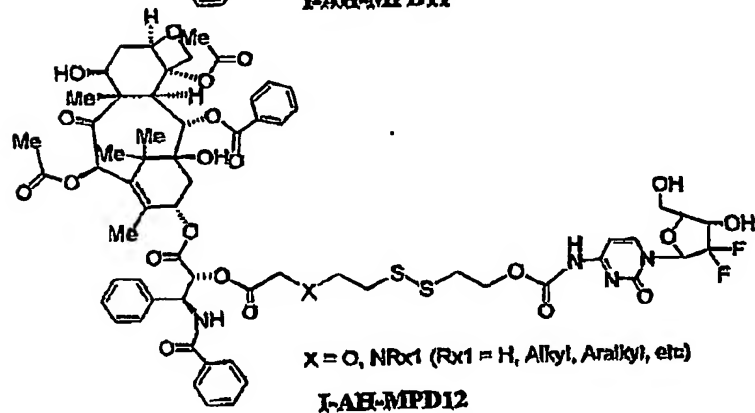


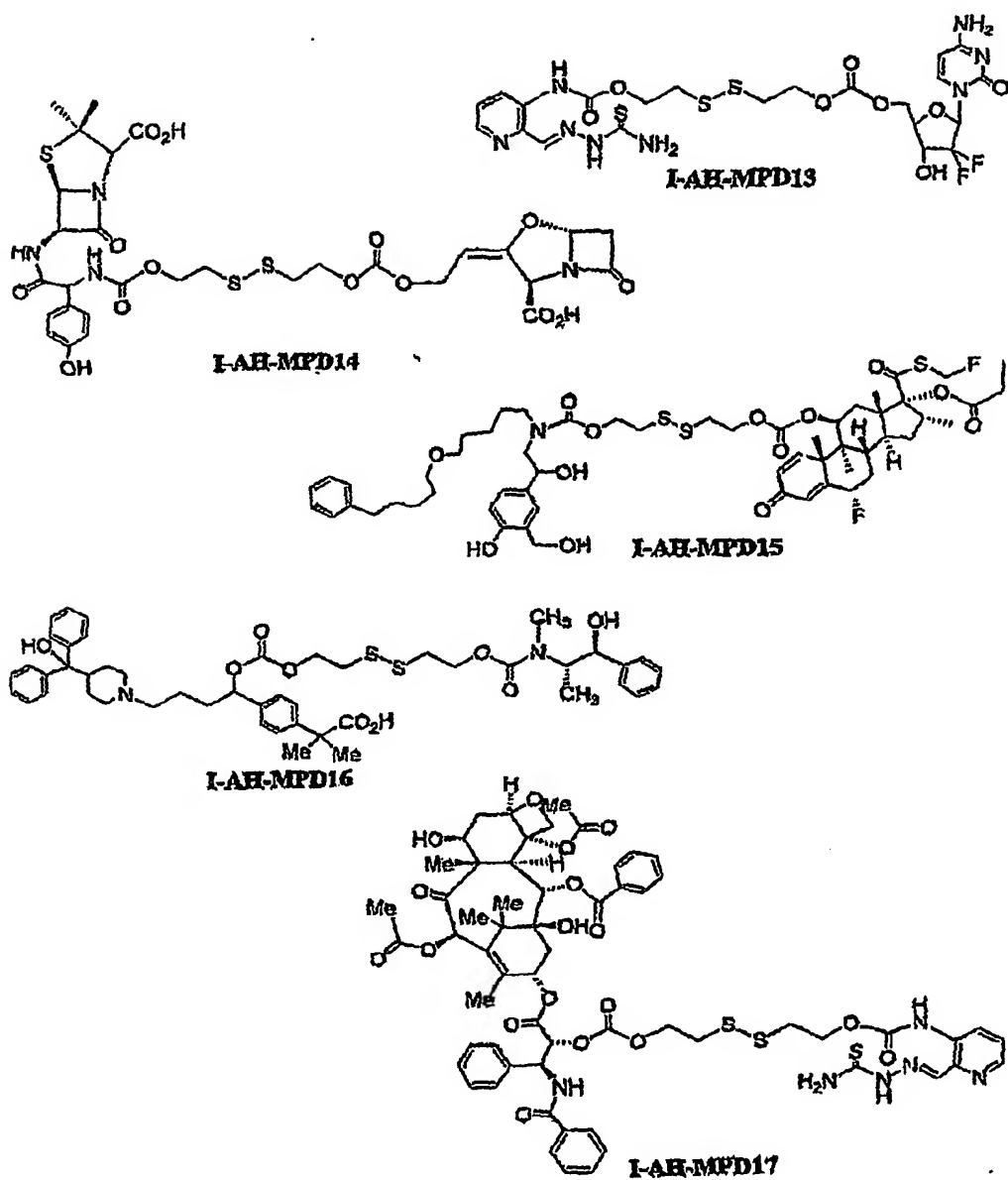
(e) Mutual prodrugs of one carboxyl-containing and one hydroxyl-containing drugs

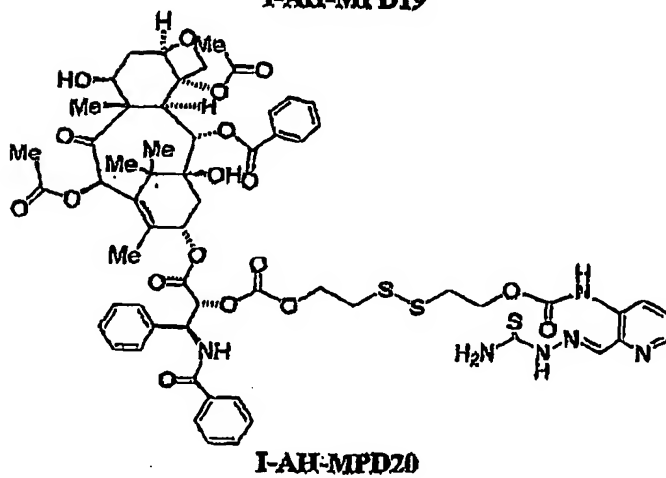
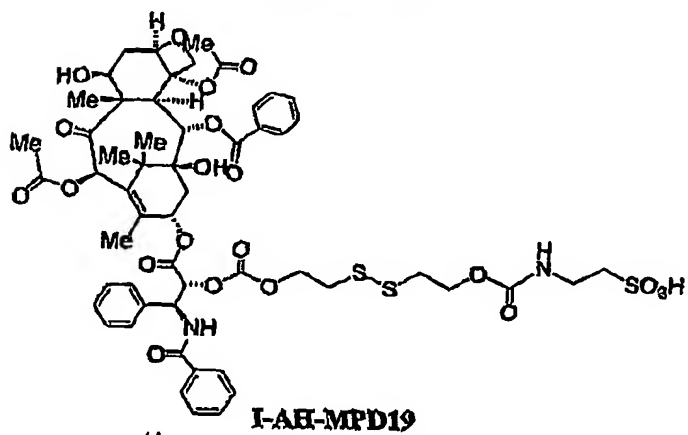
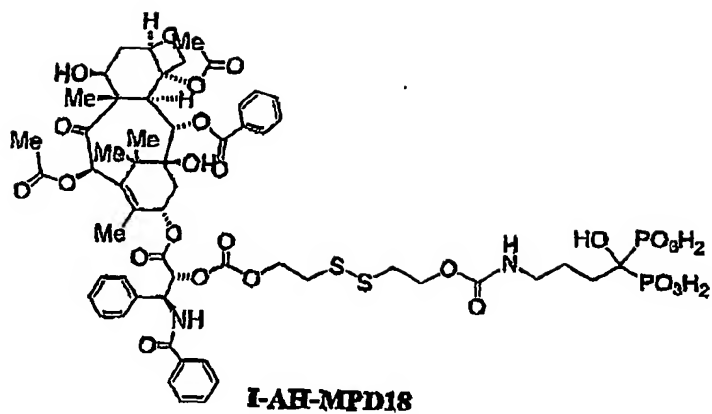


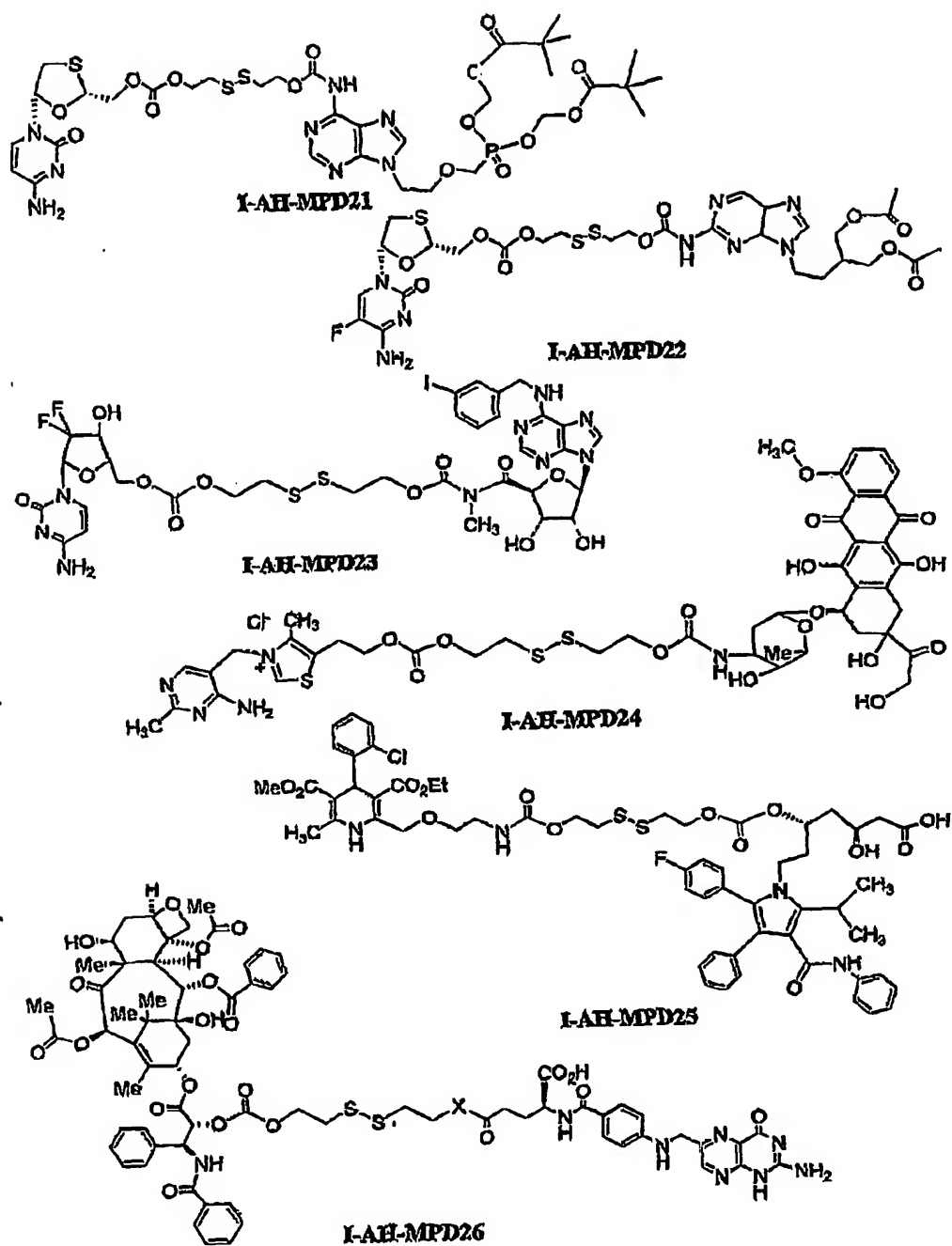
(f) Mutual prodrugs of one amino-containing and one hydroxyl-containing drugs



**I-AH-MPD9****I-AH-MPD10****I-AH-MPD11****I-AH-MPD12**







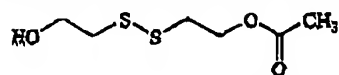
Another embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I selected from the group consisting of I-C1-PD1, I-C1-PD2, I-C1-PD3, I-C1-PD4, I-C1-PD4b, I-C1-PD5, I-C1-PD6, I-C1-PD7, I-C1-PD8, I-C1-PD9, I-C1-PD10, I-C1-PD11, I-C1-PD12, I-C1-KM, I-C1-PD14, I-C1-PD15a, I-C1-PD15b, I-A1-PD1, I-A1-PD2, I-A1-PD3, I-A1-PD4, I-A1-PD5, I-A1-PD6, I-A1-PD7, I-A1-PD8, I-A1-PD9, I-A1-PD10, I-A1-PD11, I-A1-PD12, I-A1-PD13, I-A1-PD14, I-A1-PD15a, I-A1-PD15b, I-A1-PD16, I-A1-PD17, I-A1-PD18, I-A1-PD19, I-A1-PD20, I-A1-PD21, I-A1-PD22, I-A1-PD23, I-A1-PD24, I-A1-PD25, I-A1-PD26, I-A1-PD27, I-A1-PD28, I-A1-PD29, I-A1-PD30, I-A1-PD31, I-A1-PD32, I-A1-PD33, I-A1-PD34, I-A1-PD35, I-A1-PD36, I-A1-PD37, I-A1-PD38, I-A1-PD39, I-A1-PD40, I-A1-PD41, I-A1-PD42, I-A1-PD43, I-A1-PD44, I-A1-PD45, I-A1-PD46, I-A1-PD47, I-A1-PD48, I-A1-PD49, I-A1-PD50, I-A1-PD51, I-A1-PD52, I-A1-PD53, I-A1-PD54, I-A1-PD55, I-A1-PD56, I-A1-PD57, I-A1-PD58, I-A1-PD59, I-A1-PD60, I-A1-PD61, I-A1-PD62, I-A1-PD63, I-A1-PD64, I-A1-PD65, I-A1-PD66, I-A1-PD67, I-A1-PD68, I-A1-PD69, I-A1-PD70, I-A1-PD71, I-A1-PD72, I-A1-PD73, I-A1-PD74, I-A1-PD75, I-A1-PD76, I-A1-PD77, I-A1-PD78, I-A1-PD79, I-A1-PD80, I-A1-PD81, I-A1-PD82, I-A1-PD83, I-A1-PD84, I-A1-PD85, I-A1-PD86, I-A1-PD87, I-A1-PD88, I-A1-PD89, I-A1-PD90, I-A1-PD91, I-A1-PD92, I-A1-PD93, I-A1-PD94, I-A1-PD95, I-A1-PD96, I-A1-PD97, I-A1-PD98, I-A1-PD99, I-A1-PD100, I-A1-PD101, I-A1-PD102, I-A1-PD103, I-A1-PD104, I-A1-PD105, I-A1-PD106, I-A1-PD107, I-A1-PD108, I-A1-PD109, I-A1-PD110, I-A1-PD111, I-A1-PD112, I-A1-PD113, I-A1-PD114, I-A1-PD115, I-A1-PD116, I-A1-PD117, I-A1-PD118, I-A1-PD119, I-A1-PD120, I-A1-PD121, I-A1-PD122, I-A1-PD123, I-A1-PD124, I-A1-PD125, I-A1-PD126, I-A1-PD127, I-A1-PD128, I-A1-PD129, I-A1-PD130, I-A1-PD131, I-A1-PD132, I-A1-PD133, I-A1-PD134, I-A1-PD135, I-A1-PD136, I-A1-PD137, I-A1-PD138, I-A1-PD139, I-A1-PD140, I-A1-PD141, I-A1-PD142, I-A1-PD143, I-A1-PD144, I-A1-PD145, I-A1-PD146, I-A1-PD147, I-A1-PD148, I-A1-PD149, I-A1-PD150, I-A1-PD151, I-A1-PD152, I-A1-PD153, I-A1-PD154, I-A1-PD155, I-A1-PD156, I-A1-PD157, I-A1-PD158, I-A1-PD159, I-A1-PD160, I-A1-PD161, I-A1-PD162, I-A1-PD163, I-A1-PD164, I-A1-PD165, I-A1-PD166, I-A1-PD167, I-A1-PD168, I-A1-PD169, I-A1-PD170, I-A1-PD171, I-A1-PD172, I-A1-PD173, I-A1-PD174, I-A1-PD175, I-A1-PD176, I-A1-PD177, I-A1-PD178, I-A1-PD179, I-A1-PD180, I-A1-PD181, I-A1-PD182, I-A1-PD183, I-A1-PD184, I-A1-PD185, I-A1-PD186, I-A1-PD187, I-A1-PD188, I-A1-PD189, I-A1-PD190, I-A1-PD191, I-A1-PD192, I-A1-PD193, I-A1-PD194, I-A1-PD195, I-A1-PD196, I-A1-PD197, I-A1-PD198, I-A1-PD199, I-A1-PD200, I-A1-PD201, I-A1-PD202, I-A1-PD203, I-A1-PD204, I-A1-PD205, I-A1-PD206, I-A1-PD207, I-A1-PD208, I-A1-PD209, I-A1-PD210, I-A1-PD211, I-A1-PD212, I-A1-PD213, I-A1-PD214, I-A1-PD215, I-A1-PD216, I-A1-PD217, I-A1-PD218, I-A1-PD219, I-A1-PD220, I-A1-PD221, I-A1-PD222, I-A1-PD223, I-A1-PD224, I-A1-PD225, I-A1-PD226, I-A1-PD227, I-A1-PD228, I-A1-PD229, I-A1-PD230, I-A1-PD231, I-A1-PD232, I-A1-PD233, I-A1-PD234, I-A1-PD235, I-A1-PD236, I-A1-PD237, I-A1-PD238, I-A1-PD239, I-A1-PD240, I-A1-PD241, I-A1-PD242, I-A1-PD243, I-A1-PD244, I-A1-PD245, I-A1-PD246, I-A1-PD247, I-A1-PD248, I-A1-PD249, I-A1-PD250, I-A1-PD251, I-A1-PD252, I-A1-PD253, I-A1-PD254, I-A1-PD255, I-A1-PD256, I-A1-PD257, I-A1-PD258, I-A1-PD259, I-A1-PD260, I-A1-PD261, I-A1-PD262, I-A1-PD263, I-A1-PD264, I-A1-PD265, I-A1-PD266, I-A1-PD267, I-A1-PD268, I-A1-PD269, I-A1-PD270, I-A1-PD271, I-A1-PD272, I-A1-PD273, I-A1-PD274, I-A1-PD275, I-A1-PD276, I-A1-PD277, I-A1-PD278, I-A1-PD279, I-A1-PD280, I-A1-PD281, I-A1-PD282, I-A1-PD283, I-A1-PD284, I-A1-PD285, I-A1-PD286, I-A1-PD287, I-A1-PD288, I-A1-PD289, I-A1-PD290, I-A1-PD291, I-A1-PD292, I-A1-PD293, I-A1-PD294, I-A1-PD295, I-A1-PD296, I-A1-PD297, I-A1-PD298, I-A1-PD299, I-A1-PD300, I-A1-PD301, I-A1-PD302, I-A1-PD303, I-A1-PD304, I-A1-PD305, I-A1-PD306, I-A1-PD307, I-A1-PD308, I-A1-PD309, I-A1-PD310, I-A1-PD311, I-A1-PD312, I-A1-PD313, I-A1-PD314, I-A1-PD315, I-A1-PD316, I-A1-PD317, I-A1-PD318, I-A1-PD319, I-A1-PD320, I-A1-PD321, I-A1-PD322, I-A1-PD323, I-A1-PD324, I-A1-PD325, I-A1-PD326, I-A1-PD327, I-A1-PD328, I-A1-PD329, I-A1-PD330, I-A1-PD331, I-A1-PD332, I-A1-PD333, I-A1-PD334, I-A1-PD335, I-A1-PD336, I-A1-PD337, I-A1-PD338, I-A1-PD339, I-A1-PD340, I-A1-PD341, I-A1-PD342, I-A1-PD343, I-A1-PD344, I-A1-PD345, I-A1-PD346, I-A1-PD347, I-A1-PD348, I-A1-PD349, I-A1-PD350, I-A1-PD351, I-A1-PD352, I-A1-PD353, I-A1-PD354, I-A1-PD355, I-A1-PD356, I-A1-PD357, I-A1-PD358, I-A1-PD359, I-A1-PD360, I-A1-PD361, I-A1-PD362, I-A1-PD363, I-A1-PD364, I-A1-PD365, I-A1-PD366, I-A1-PD367, I-A1-PD368, I-A1-PD369, I-A1-PD370, I-A1-PD371, I-A1-PD372, I-A1-PD373, I-A1-PD374, I-A1-PD375, I-A1-PD376, I-A1-PD377, I-A1-PD378, I-A1-PD379, I-A1-PD380, I-A1-PD381, I-A1-PD382, I-A1-PD383, I-A1-PD384, I-A1-PD385, I-A1-PD386, I-A1-PD387, I-A1-PD388, I-A1-PD389, I-A1-PD390, I-A1-PD391, I-A1-PD392, I-A1-PD393, I-A1-PD394, I-A1-PD395, I-A1-PD396, I-A1-PD397, I-A1-PD398, I-A1-PD399, I-A1-PD400, I-A1-PD401, I-A1-PD402, I-A1-PD403, I-A1-PD404, I-A1-PD405, I-A1-PD406, I-A1-PD407, I-A1-PD408, I-A1-PD409, I-A1-PD410, I-A1-PD411, I-A1-PD412, I-A1-PD413, I-A1-PD414, I-A1-PD415, I-A1-PD416, I-A1-PD417, I-A1-PD418, I-A1-PD419, I-A1-PD420, I-A1-PD421, I-A1-PD422, I-A1-PD423, I-A1-PD424, I-A1-PD425, I-A1-PD426, I-A1-PD427, I-A1-PD428, I-A1-PD429, I-A1-PD430, I-A1-PD431, I-A1-PD432, I-A1-PD433, I-A1-PD434, I-A1-PD435, I-A1-PD436, I-A1-PD437, I-A1-PD438, I-A1-PD439, I-A1-PD440, I-A1-PD441, I-A1-PD442, I-A1-PD443, I-A1-PD444, I-A1-PD445, I-A1-PD446, I-A1-PD447, I-A1-PD448, I-A1-PD

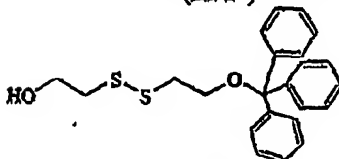
MPD23₇ I-AA-MPD24, I-AA-MPD25; I*AA-MPD26₅ I-AA-MPD27, WX-MPDI, I-CC-MPD2, I-CC-MPD3, I-CC-MPD4, I-CC-MPD5, I-CC-MPD6, I-HH-MPD1, I-HH-MPD2, I-HH-MPD3, I-HH-MPD4, I-HH-MPD5, MIH-MPD6, I-HH-MPD7, I-HH-MPD8, I-HH-MPD9, I-HH-MPD10, I-HH-MPD11, I-HH-MPD12, I-HH-MPD13, I-HH-MPDH₁, I-HH-MPD15, I-HH-MPD16, I-HH-MPD17, I-HH-MPD18* I-HHAH-TMPDJ, I-CA-MPD1, I-CA-MPD2, I-CA-MPD3» I-CA-MPD4, I-CA-MPD5, I-CA-MPD6, I-CA-MPD7_a I-CA-MPD8, I-CA-MPD[^] I-CA-MPD10, I-CA-MPD11, I-CA-MPD12, I-CA-MPD13, I-CA-MPD14, I-CA-MPD15_» I-CA-MPD16, I-CA-MPD17, I-CA-MPD18, I-CA-MPDJ₉, I-CA-MPD20, I-CA-MPD21, I-CA-MPD22, I-CA-MPD23, I-CA-MPD24, I-CA-MPD25, I-CA-MPD26, I-CA-MPD27₅ I-CA-MPD28, I-CA-MPD29, I-CA-MPD30, I-AH-MPDI₅ I-AH-MPD2, I-AH-MPD3, I-AH-MPD4, I-AH-MPD5, I-AH-MPD6, I-AH-MPD7, I-AH-MPD8, I-AH-MPD[^] I-AH-MPD10, I-AH-MPD11, I-AH-MPD12, I-AH-MPD13, I-AH-MPD14, I-AH-MPD15, I-AH-MPD16, I-AH-MPD17, I-AH-MPD18, I-AH-MPD19, I-AH-MPD20, I-AH-MPD21, I-AH-MPD22, I-AH-MPD23, I-AH-MPD24, I-AH-MPD25, I-AH-MPD26, I-CH-MPDI₁ I-CH-MPD2, I-CH-MPD3, I-CH-MPD4_» I-CH-MPDS, and I-CH-MPD6 or a pharmaceutical salt thereof and on© or *note* pharmaceutically acceptable earners, vehicles or diluents.

An embodiment of the invention is a method of treating a *mmaml* or human in need thereof comprising administering a therapeutically effective amount of the pharmaceutical composition comprising the compound of formula I.

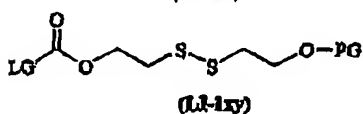
Another embodiment of the invention is the below listed novel intermediates:



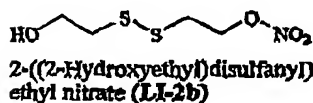
2-((2-Hydroxyethyl)disulfanyl)ethyl acetate
(LI-1a)



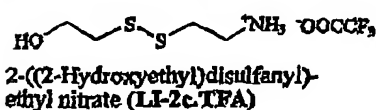
2-((2-(Trityloxy)ethyl)disulfanyl)ethanol
(LI-1c)



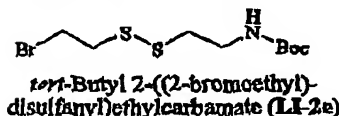
(LI-1xy)



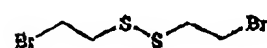
2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2b)



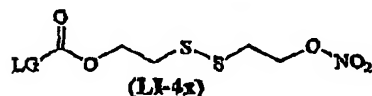
2-((2-Hydroxyethyl)disulfanyl)ethyl nitrate (LI-2c.TFA)



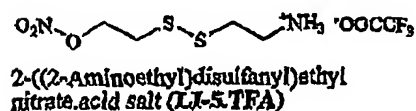
tert-Butyl 2-((2-bromoethyl)disulfanyl)ethyl carbamate (LI-2e)



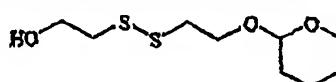
1,2-Bis(2-bromoethyl)disulfane (LI-3a)



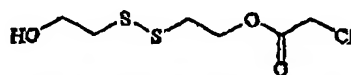
(LI-4x)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate acid salt (LI-5.TFA)



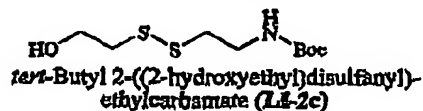
2-((2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)disulfanyl)ethanol (LI-1b)



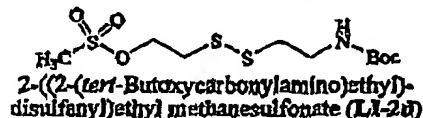
2-((2-Hydroxyethyl)disulfanyl)ethyl 2-chloroacetate (LI-1d)



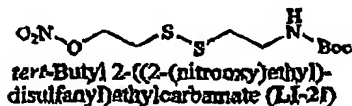
2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)



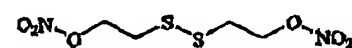
tert-Butyl 2-((2-hydroxyethyl)disulfanyl)ethyl carbamate (LI-2c)



2-((2-(tert-Butoxycarbonylamino)ethyl)disulfanyl)ethyl methanesulfonate (LI-2d)



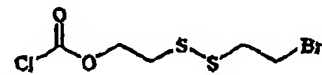
tert-Butyl 2-((2-(nitrooxy)ethyl)disulfanyl)ethyl carbamate (LI-2f)



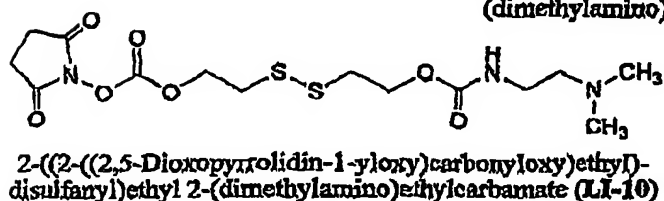
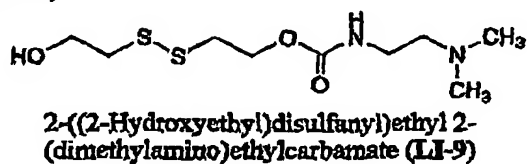
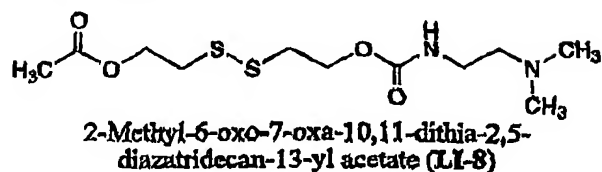
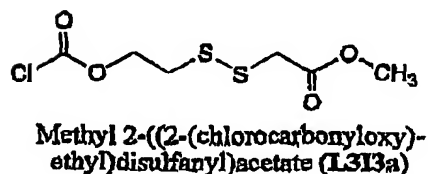
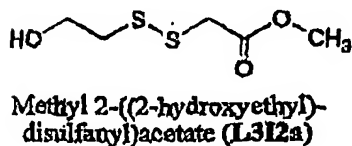
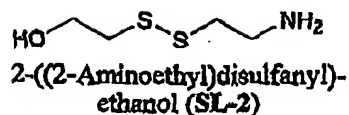
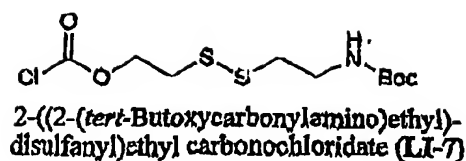
2,2'-Disulfanediybis(ethane-2,1-diyl) dinitrate (LI-3b)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)



2-((2-Bromoethyl)disulfanyl)ethyl carbonochloridate (LI-6)



A further embodiment of the invention is use of the above listed novel intermediates in the processes for the preparation of compounds of formula I.

Further embodiments include methods of preparation and methods of use of compounds of formula (I) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is process for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof wherein the process comprises of:

10 monoprotection of Bis-(2-hydroxyethyl)disulfide (SL-I) with 3» appropriate hydroxyl protecting group to give a corresponding monoprotected intermediate,

conversion of the corresponding monoprotected intermediate to an activated formyl intermediate by treating with phosgene or its equivalent* and

reaction of the activated formyl intermediate with an appropriate amino- or hydroxy containing D¹ to give the corresponding compound of formula I.

- 5 Another embodiment of the invention is a process for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the process comprises of:

-converting carboxy containing P I into an activated intermediate comprising acyl halide, imidazoline or isocyanate, and

- 10 -reacting the activated intermediate with a linker intermediate to obtain the compound of formula I.

In another embodiment, the invention is a process in which the monoprotected intermediate is LIIx, and the activated formyl intermediate is LIIxy,

- 15 Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D* is NO₂ or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated DI with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) in a suitable solvent in presence of a suitable coupling agent

- 20 Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D¹ is NO₂ or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) into its formyl halide or imidazolide (LI-4x) by using a phosgene or its equivalent reagent and reacting the resulting reactive intermediate with a suitable amino- or hydroxy-containing drug in suitable solvent in presence of a suitable base.

- 25 Another embodiment of the invention is a process for preparation of compounds of formula (I), wherein D² is NO⁺ or pharmaceutically acceptable salt thereof, wherein the process comprises, joining/reacting a selectively protected and activated drug with a solution of 2-((2-iodoethyl)dithio)ethyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base.

Another embodiment of the invention is a process for preparation of mutual prodrugs of compounds of formula (I), or pharmaceutically acceptable salts thereof, wherein a process comprises,

- A) iponoprotection of Bis-(2-hydroxyethyl)disulphide (SL-I) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LHx,
- B) reaction of formyl linker intermediate LI-lxy with amino or hydroxyl containing drug (D') to obtain, the prodrug of formula I with free hydroxyl group on the linker,
- C) conversion of the intermediate obtained in the step B into activated bromide or imidazoline derivative, and
- D) reaction of the intermediate obtained in the step C with the drug D* to obtain the mutual prodrug of formula I.

Further embodiments of the invention are processes for the preparation of compounds of formula I, or pharmaceutically acceptable salts thereof, wherein the processes comprise of the steps that are generally depicted in the schemes 1-23.

- Further embodiments include the pharmaceutical composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

- Another embodiment of the invention is use of compounds of formula I or pharmaceutically acceptable salt thereof, in the treatment of disease conditions originally treatable by the corresponding free drug(s)

- It should be understood that while this Invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given method, process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. The contents of the articles, patents, and patent applications, and all other documents mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically individually indicated to be incorporated by reference.

Yet another embodiment of the invention is a compound of formula I containing an amino-containing therapeutic agent selected from the group consisting of: I-AA-MPD1, I-AA-MPD2, I-AA-MPD3, and I-AA-MPD4.

Another embodiment of the invention is a double prodrug of formula (I) selected from the group consisting of: I-AA-MPD5, I-AA-MPD6, I-AA-MPD7, and I-AA-MPD8.

The present invention also provides mutual prodrugs of formula (I) selected from the group consisting of: I-CA-MPD1, I-CA-MPD2, I-CA-MPD3, I-CA-MPD4, I-CA-MPD5, I-CA-MPD6, I-CA-MPD7, I-CA-MPD8, I-CA-MPD9, I-CA-MPD10, I-CA-MPD11, I-CA-MPD12, I-CA-MPD13, I-CA-MPD14, I-CA-MPD15, I-CA-MPD16, I-CA-MPD17, I-CA-MPD18, I-CA-MPD19, I-CA-MPD20, I-CA-MPD21, I-CA-MPD22, I-CA-MPD23, I-CA-MPD24, I-CA-MPD25, I-CA-MPD26, I-CA-MPD27, I-CA-MPD28, I-CA-MPD29, and I-CA-MPD30.

In another embodiment, the invention provides compounds of formula (J) selected from the group of mutual prodrugs made from an amino-containing therapeutic agent and a hydroxyl-containing therapeutic agent such as: I-AH-MPD1, I-AH-MPD2, I-AH-MPD3, I-AH-MPD4, I-AH-MPD5, I-AH-MPD6, I-AH-MPD7, I-AH-MPD8, I-AH-MPD9, I-AH-MPD10, I-AH-MPD11, I-AH-MPD12, I-AH-MPD13, I-AH-MPD14, I-AH-MPD15, I-AH-MPD16, I-AH-MPD17, I-AH-MPD18, I-AH-MPD19, I-AH-MPD20, I-AH-MPD21, I-AH-MPD22, I-AH-MPD23, I-AH-MPD24, I-AH-MPD25, and I-AH-MPD26.

Yet another embodiment of the invention relates to compounds of formula (K) of mutual prodrugs made from a hydroxyl-containing therapeutic agent and a hydroxyl-containing therapeutic agent such as: I-RH-MPD1, I-HH-MPD2, I-HH-MPD3, I-HH-MPD4, I-HH-MPD5, I-HH-MPD6, I-HH-MPD7, I-HH-MPD8, I-HH-MPD9, I-HH-MPD10, I-HH-MPD11, I-HH-MPD12, I-HH-MPD13, I-HH-MPD14, I-HH-MPD15, I-HH-MPD16, I-HH-MPD17, and I-HH-MPD18.

The present invention also provides compounds of formula (I) containing water-soluble prodrugs of insoluble or sparingly-soluble therapeutic agents such as: I-HI-PD1, I-HI-PD2, I-HI-PD3, I-HI-PD4, I-HI-PD5, I-HI-PD6, I-HI-PD7, I-HI-PD8, I-HI-PD9, I-HI-PD10, I-HI-PD11, I-HI-PD12, I-HI-PD13, I-AI-PD1, I-AI-PD2, I-AI-PD3, I-AI-PD4, I-AI-PD5, I-AI-PD6, I-AI-PD7, I-AI-PD8, I-AI-PD9, I-AI-PD10, I-AI-PD11, I-AI-PD12, I-AI-PD13, I-AI-PD14, I-AI-PD15A, I-AI-PD15B, I-AI-

10 C1-NOPP6, Ĩ-C1-NOPD7, U-C1-NO)PDSa₅ 1-C1-NOPD8b, I-C1-NOPD9, 1-C1-NOPD10, J-C1-NOPDJa, I-C1^N0PD13, 1-c μNOPD14a, I-C1-NOPDMb₅ 1-C1-NOHUSb, I-C1-N0PD16, I-Cī-NOPM7a, I-C1-N0PD17b₇ I-C1-NOPD18, I-C1-N0PD19, X-C1-NOPD20a, I-C μNOPD20b, X-C1-N0PD2 Ĩ, Ĩ-C1-NOPD22, J-C1-NOPD23b, I^C1-NOPD24, Ĩ-C1-N0PD2S. I-CI-NOPD26, 1-A1-NOPDI, Ĩ-A1-N0PD2, Ĩ-A1-NOPD3A, 15 I-A1-NOPD3B, I-A1-NOPD4, tA1-NOPDS, 1-A1-N0PD6, Ĩ-A1-NOPD7, I^*M-NOPD8, I-A1-NOPD9, I-A1-HOPDIOa, I-A1-NOPDIOb, I-A2-N0PDK I-^NOPDib, ĩ»A2-N01?D2a, I-A2-NOFD2b, I-A3-NOPDla, I-A3-NOPD Ĩb, I-A3-N0PD2a, ĩ-A3 «NOPD2b, I-H1-NOPDI, 1-H1-NOPD29, l>Bl«N0PD2b, I-H1-NOPD3, 1-H1-N0PD4, 1-HI-NOPDSb, I-H1-N0PD6, 1-H1-N0PD7, Ĩ-H1-N0PDS, I-HI-NOPD9, 20 ĩ-HI-NOPm θ.

25 derivatives of aspirin, fentanyl, beta blockers, statins or nitroglycerin calcium channel blockers. Suitable drugs are described in the literature such as the Merck index, ID#100. Prous Sciences integrity*, Prous Science Owgs of the Future™. The Efficacy of the like.

30 «std to treat other diseases such as cardiovascular diseases, selected from beta adrenergic blockers, calcium chanael blockers, angiotensin U receptor antagonists, antithrombotics,

BMGCoA reductase inhibitors, aspirin or nitrooxy derivatives of aspirin, nitrosated beta blockers, nitrosated or nitrosilated calcium channel blockers. Pharmaceutical compositions containing two or more of compounds of the invention can be used for the purpose of combination therapy. These pairs of compounds of invention; can be from the same therapeutic area or from different therapeutic areas for treating one or more diseases or conditions.

If the compounds of the invention, which have one or more asymmetric carbon atoms, can exist as the optically pure enantiomers, pure diastereoisomers, enantiomer racemic mixtures, diastereoisomer racemic mixtures, racemates or racemate mixtures, Within the scope of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (T).

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula (C) or pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention relates to the pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and at least another pharmaceutically active compound. The pharmaceutically active compound can be from the same or different therapeutic areas for treating one or more disease conditions) together with one or more pharmaceutically acceptable carriers, vehicles or diluents.

Further embodiments include methods of use of compounds of formula (I) or pharmaceutically acceptable salts thereof.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein the process comprises, mixing a selectively protected and activated ring with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate in a suitable solvent in presence of a suitable coupling agent. Another embodiment of the invention is a compound or intermediate generated in the above methods and processes.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein a process comprises, converting 2-((2-hydroxyethyl)dithio)ethyl nitrate into its formyl halide or imidazolide by

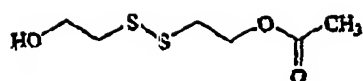
using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable drug in suitable solvent *in* presence of a suitable base.

Another embodiment of the invention is a process for preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, wherein the process comprises,
 5 mixing/reacting a selectively protected, and activated drug with a solution of 2-((2-aminoethyl)ditbio)ethyl nitrate (or its acid salt) in a suitable solvent in presence of a suitable coupling agent and/or base.

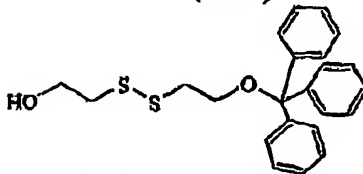
Another embodiment of the invention comprises the novel intermediates formed in the preparation of present invention, Further embodiments include a pharmaceutical
 10 composition comprising a therapeutically effective amount of novel intermediates or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.

Another embodiment of the invention is processes for the preparation of compounds of formula (I) or pharmaceutically acceptable salt thereof, as well as the
 15 starting materials and intermediates involved as depicted in schemes 1-23.

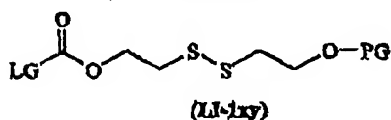
Another embodiment of the invention comprises the novel intermediates obtained in the preparation of compounds of formula I, where the intermediates are selected from:



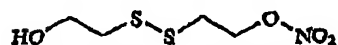
2-((2-Hydroxyethyl)disulfanyl)ethyl acetate
(LI-1a)



2-((2-(Trityloxy)ethyl)disulfanyl)ethanol
(LI-1c)



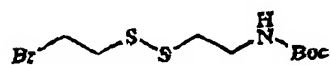
(LI-1xy)



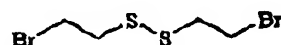
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2b)



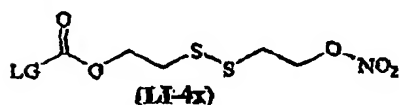
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2c.TFA)



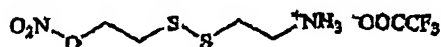
tert-Butyl 2-((2-bromoethyl)-
disulfanyl)ethyl carbamate (LI-2e)



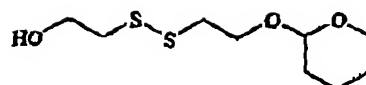
1,2-Bis(2-bromoethyl)disulfane (LI-3a)



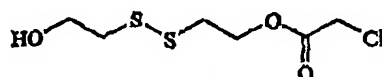
(LI-4x)



2-((2-Aminoethyl)disulfanyl)ethyl
nitrate acid salt (LI-5.TFA)



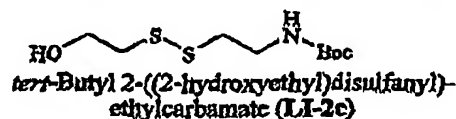
2-((2-(Tetrahydro-2H-pyran-2-
yloxy)ethyl)disulfanyl)ethanol (LI-1b)



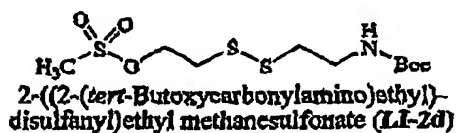
2-((2-Hydroxyethyl)disulfanyl)ethyl
2-chloroacetate (LI-1d)



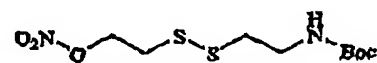
2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)



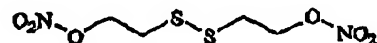
tert-Butyl 2-((2-hydroxyethyl)disulfanyl)-
ethyl carbamate (LI-2c)



2-((2-(tert-Butoxycarbonylamino)ethyl)-
disulfanyl)ethyl methanesulfonate (LI-2d)



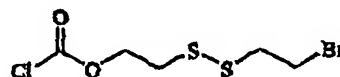
tert-Butyl 2-((2-(nitrooxy)ethyl)-
disulfanyl)ethyl carbamate (LI-2f)



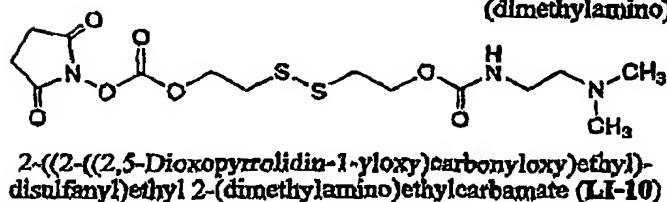
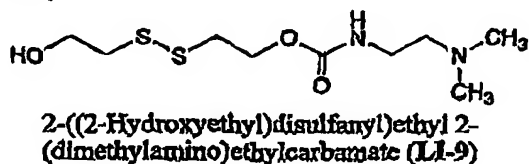
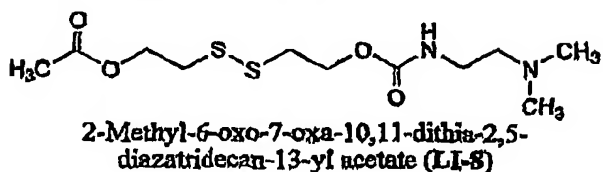
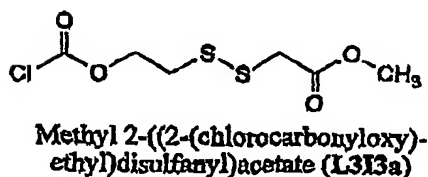
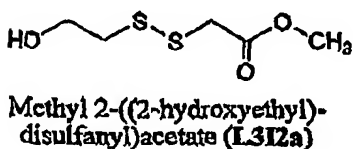
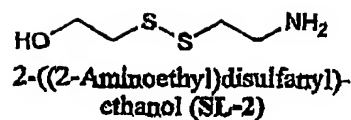
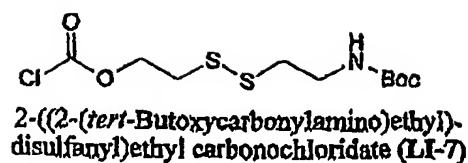
2,2'-Disulfanediyldis(ethane-2,1-diyl)-
dinitrate (LI-3b)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)



2-((2-Bromoethyl)disulfanyl)ethyl
carbonochloridate (LI-6)



Another embodiment of the invention is a mixture of compounds of formula (I) or pharmaceutically acceptable salts thereof in the treatment of disease conditions originally treatable by the corresponding free drugs.

- 5 Another embodiment of the invention includes but not limited to a pharmaceutical composition comprising the compounds of formula (I), or pharmaceutically acceptable salt thereof, selected from the group of NO-releasing prodrugs described herein, or more pharmaceutically acceptable carriers, vehicles or diluents.

- 10 It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material,

process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow. The contents of the articles, patents, and patent applications, and all other
 5 documents mentioned or cited herein, are hereby incorporated by reference to their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

POTENTIAL EXAMPLES OF MUTUAL PRODRUGS/CODRUGS:

Mutual prodrugs made from an amino-containing therapeutic agent and another
 10 amino-containing therapeutic agent;

A Mutual Prodrug of desloratadine and pseudoephedrine (I-AA-MPD1) is proposed as a potential treatment option for seasonal allergic rhinitis (SAR). Desloratadine (an active metabolite of loratadine) is a new, non-sedating, long-acting histamine antagonist and has been shown effective in the treatment of nasal and
 15 nasal symptoms associated with SAR. Pseudoephedrine is an oral decongestant

A Mutual Prodrug of amlodipine (Pfizer's Norvasc[®]) and lisinopril (Zeneca's Zestril[®]) (I-AA-MPD2) is proposed, as a potential treatment option for hypertension and congestive heart failure. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent. Lisinopril is an angiotensin-converting enzyme
 20 (ACE) inhibitor and is used for the treatment of hypertension and congestive heart failure. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of these drugs.

A Mutual Prodrug of amlodipine (Pfizer's Norvasc[®]) and losartan (Merck's Cozaar[®]) (I-AA-MPD3a) is proposed as a potential treatment option for mild to
 25 moderate hypertension. Amlodipine is a calcium channel blocker and is used as an antihypertensive and antianginal agent. Losartan potassium is an angiotensin II blocker and is used for the treatment of hypertension. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using either of these drugs.

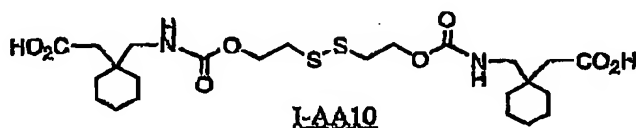
30 Examples of mutual prodrugs and double prodrugs of valdecoxib and celecoxib containing a disulfide linker are: I-AA-MPD4 and I-AA-MPD5.

Examples of double prodrugs of valdecoxib or celecoxib containing no disulfide linkers: I-AA-MPD6, I-AA-MH7, I-AA-MH8.

5 A Mutual Prodrug of fluoxetine (Lilly's Prozac®) and olanzapine (Lilly's Zyprexa®) (I-AA-MPD9) is proposed for potential treatment of patients with Bipolar disorder. Fluoxetine and Olanzapine are used in combination to treat patients with bipolar disorder while being spared the treatment-emergent mania that such patients often get on antidepressant monotherapy.

Example of double prodrug of gabapentin is proposed as potential antiepileptic agent: I-AA-MPD10.

10

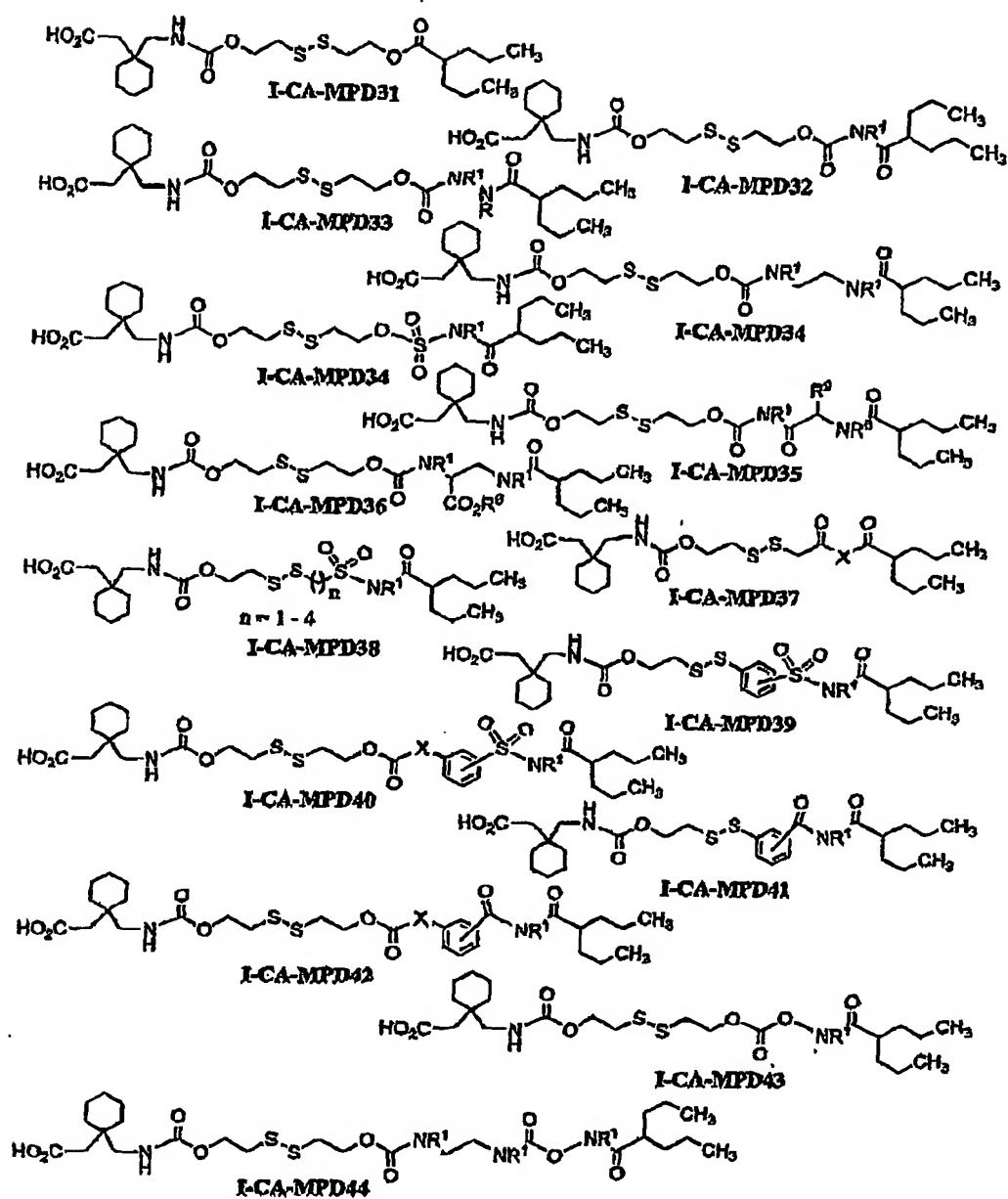


Mutual prodrugs made from an amide-containing therapeutic agent and a carbonyl-containing therapeutic agent:

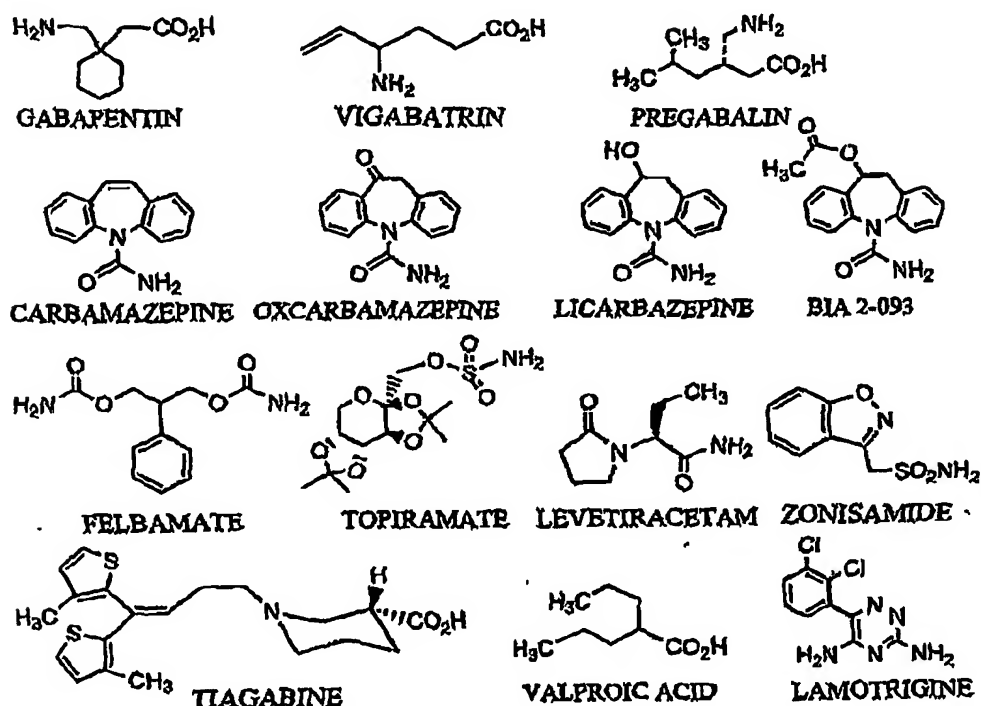
15 A mutual prodrug of cetirizine and pseudoephedrine (I-CA-MPD1) is proposed for treatment of rhinitis. Cetirizine is an antihistamine and pseudoephedrine is a nasal decongestant.

Mutual prodrugs of gabapentin and valproic acid are potential antiepileptic agents. The same kind of prodrug may be a potential treatment option for patients with bipolar disorder or other mental illnesses. The following are some of the examples:

20



Other illustrative examples of mutual prodrugs under this category include the following: Mutual prodrugs of valproic acid and other carboxyl-, hydroxy-, and aryl-containing (including amide-, and sulfonamide-containing) anticonvulsant agents such as Jevetiracetam, lamotrigine, pregabalin, carbamazepine, oxcarbazepine, licarbazepine, felbamate, fopiramate and the like. (Structures are given below). The list also includes investigational antiepileptic agents such as antipamizole, licarbazepine, Eslicarbazepine Acetate (BM. 2-093), fluorofelbamate, isovaleramide (NPS 3776), jetigibine p-23129), safbamide (NW-1015), topiramate (STP), talampanel (TLP), (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide 83alpha (ucb 34714), valrocidol (JV 1901), and the like.



Mutual Prodrugs can be made from combination of any two anti-convulsant agents listed above or any other suitable anticonvulsant agent.

Mutual prodrug of gabapentin and tiagabine (J-CA-MPD22) is proposed for potential treatment option for neurological pain and inflammation.

Mutual prodrugs made from an amino-containing therapeutic agent and a hydroxyl-containing therapeutic agent:

Mutual prodrugs of norfloxacin and metronidazole (1-AH-MPD1, 1-AH-MPD2, 1-AH-MPD3) are proposed for potential treatment of diarrhea and dysentery of bacterial, amoebic and mixed origin. Metronidazole is an antianaerobic agent and used in combination with antibiotics such as norfloxacin, ciprofloxacin, etc. for the treatment of patients with diarrhea and dysentery of bacterial, amoebic and mixed origin.

A mutual prodrug of loperamide and norfloxacin (1-AH-MPD4) is proposed for potential treatment of diarrhea and dysentery.

10 A mutual prodrug of valdecoxib and tramadol (1-AH-MPD5 and 1-AH-MPD6) as a potential therapy in postoperative pain management

A mutual prodrug of gabapentin and tramadol (1-AH-MPD7) is proposed for potential treatment of neuropathic pain after spinal cord injury.

15 A mutual prodrug of venlafaxine and paroxetine (1-AH-MPD8) is proposed for potential treatment of neurological and depression related disorders.

Mutual prodrugs made from a hydroxyl-containing therapeutic agent and another hydroxyl-containing therapeutic agent

20 Mutual prodrugs of zidovudine (AZT/Retrovir) and lamivudine (3TC/Epivir) (1-HH-MPD1, 1-HH-MPD2) are proposed as a potential treatment option for HIV and other viral infections.

POTENTIAL EXAMPLES OF WATER-SOLUBLE PRODRUGS:

Water-soluble prodrugs of insoluble/sparingly soluble therapeutic agents can be prepared using the same linker technology.

25 Water-soluble prodrugs of metronidazole include: 1-H1-PD-2, 1-H1-PP-3, 1-H1-PD-4.

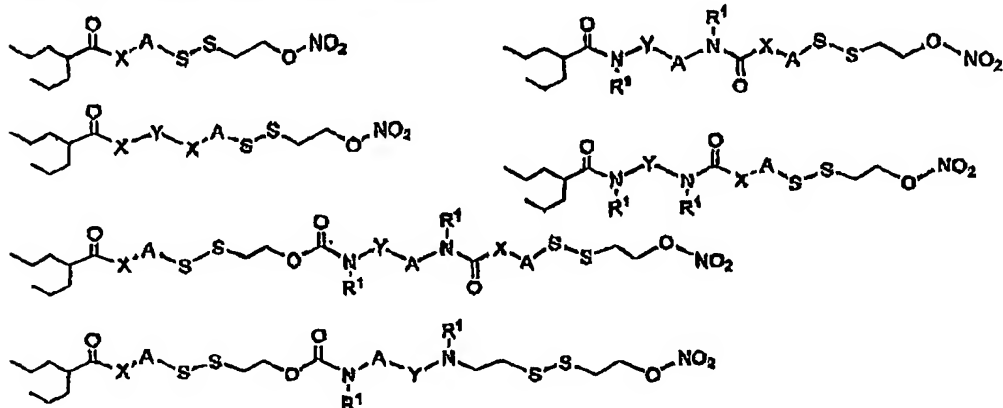
Water-soluble prodrugs of valdecoxib include: 1-A3-PD1, 1-A3-PD2a, 1-A3-PD2b, 1-A3-PD3a, 1-A3-PD3b, 1-A3-PD4, 1-A3-PD5, 1-A3-PD6, and 1-A3-PD7b.

30 Water-soluble prodrugs of paclitaxel include: 1-Taxol-PD1, 1-Taxol-PD2, 1-Taxol-PD3, 1-Taxol-PD4, 1-Taxol-PD5, 1-Taxol-PD6, and 1-S23-PD1.

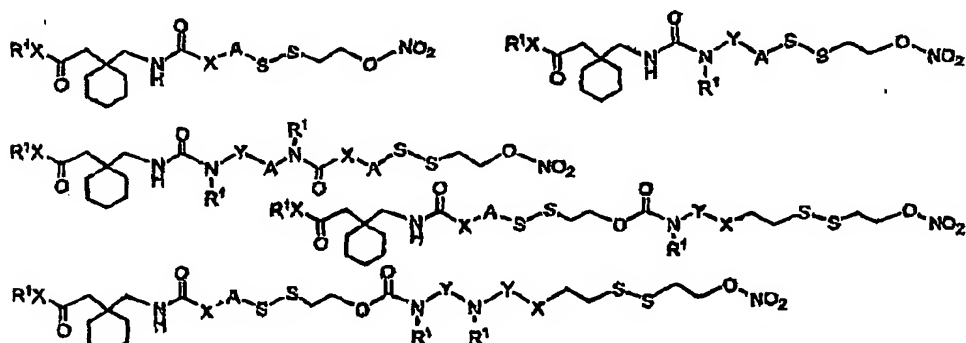
POTENTIAL EXAMPLES OF NO-RELEASING PRODRUGS:

In the following potential examples, X is O, NR^1 ($\text{R}^1 = \text{H}$, alkyl) or a bond; Y is CO, SO_2 , $\text{P}(=\text{O})\text{XR}^1$ or bond; R^1 is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or $(\text{CH}_2)_o$ ($o = 0-6$) and m is 1-2 unless otherwise stated;

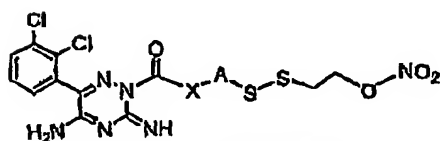
Prodrugs of Valproic Acid (Anticonvulsant):



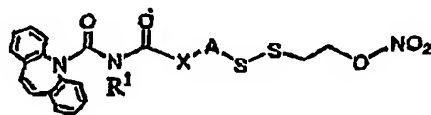
DRUGS CONTAINING REACTIVE PRIMARY AND SECONDARY AMINES, AMIDE-NH, UREA-NH, SULFONAMIDE-NH, SULFAMATE-NH, AND CARBAMATE-NH:



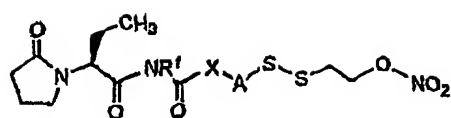
Prodrugs of Gabapentin (Anticonvulsant):



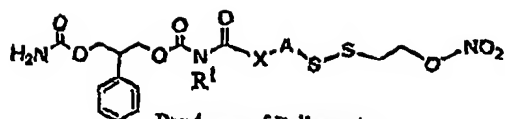
Prodrugs of Lamotrigine
(Anticonvulsant):



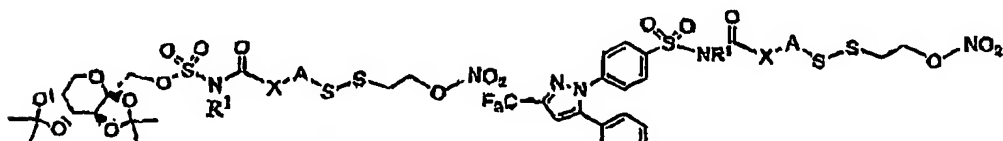
Prodrugs of Carbamazepine
(Anticonvulsant):



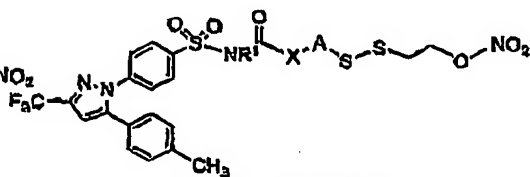
Prodrugs of Levallracetam
(Anticonvulsant):



Prodrugs of Felbamate
(Anticonvulsant):

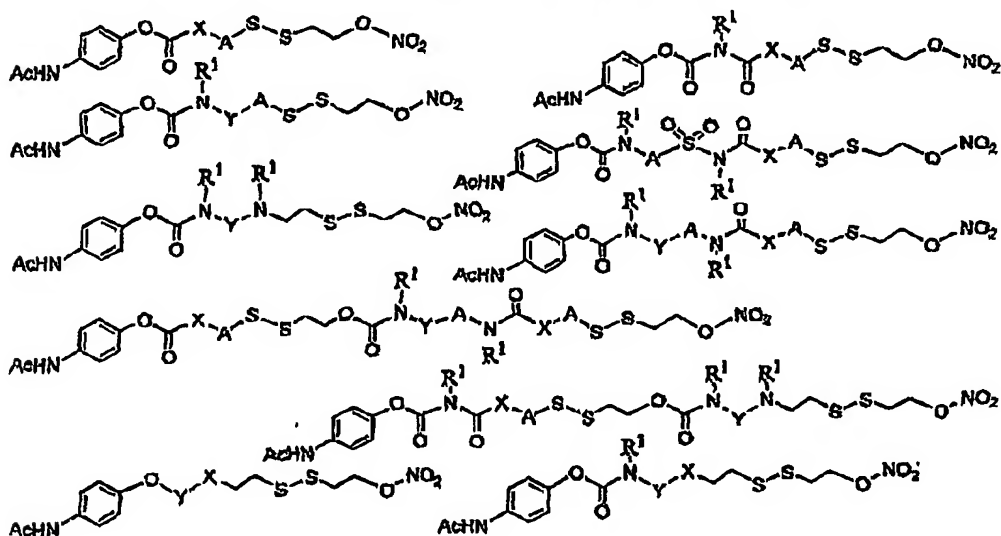


Prodrugs of Topiramate
(Anticonvulsant):



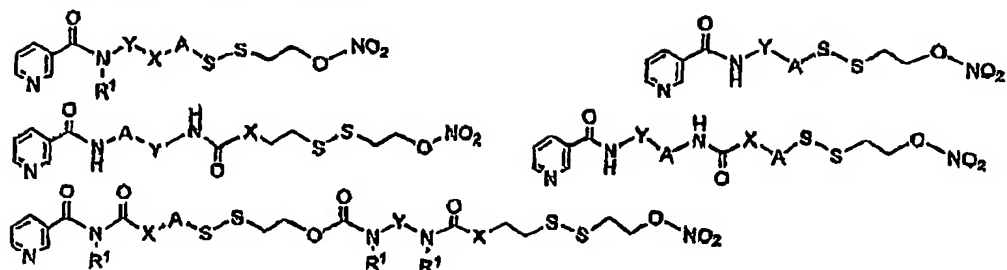
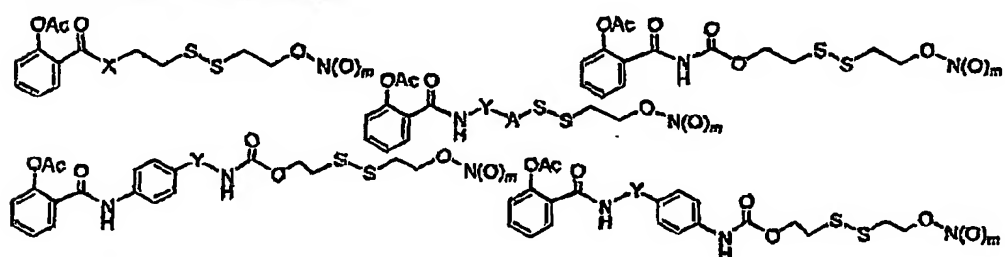
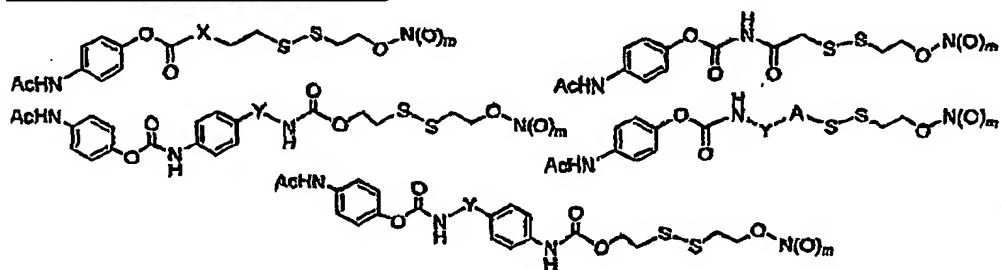
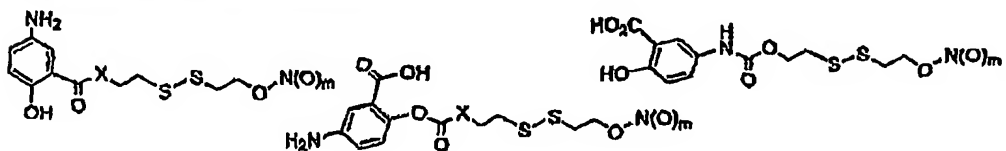
Prodrugs of Celecoxib
(Cox-2 Inhibitor):

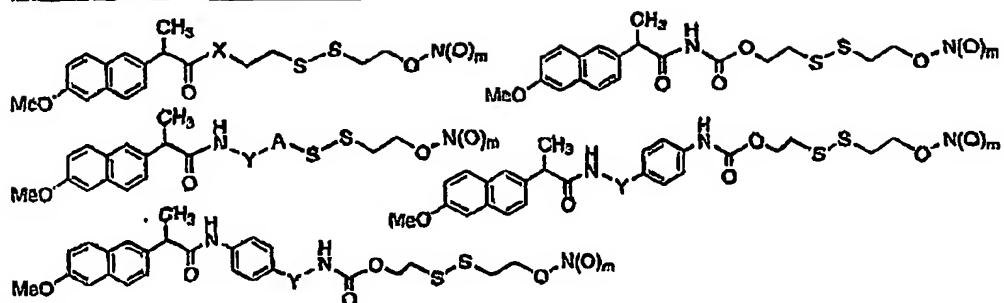
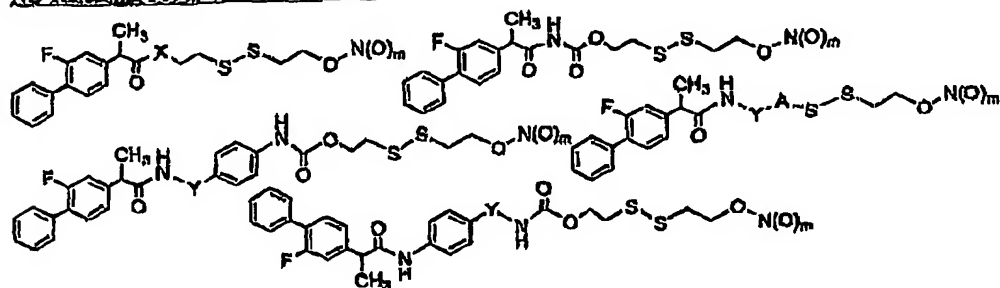
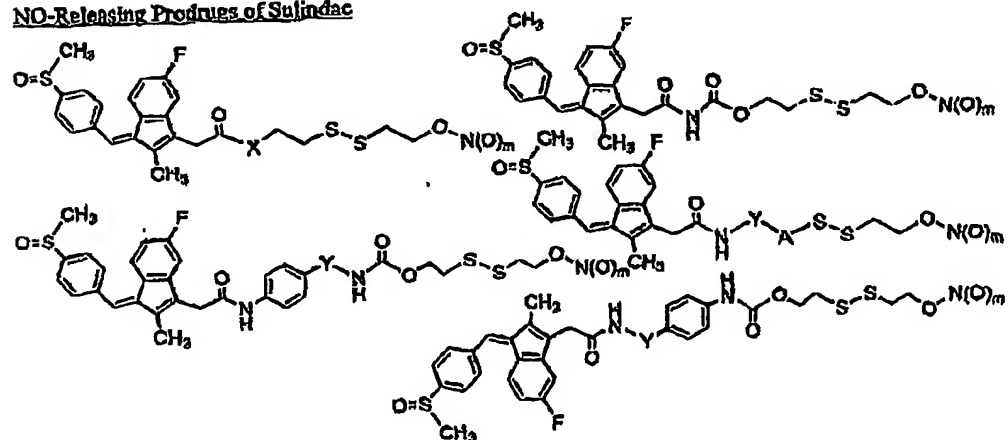
NO-Releasing Prodrugs of Paracetamol/Acetaminophen (Analgesic and Antipyretic):

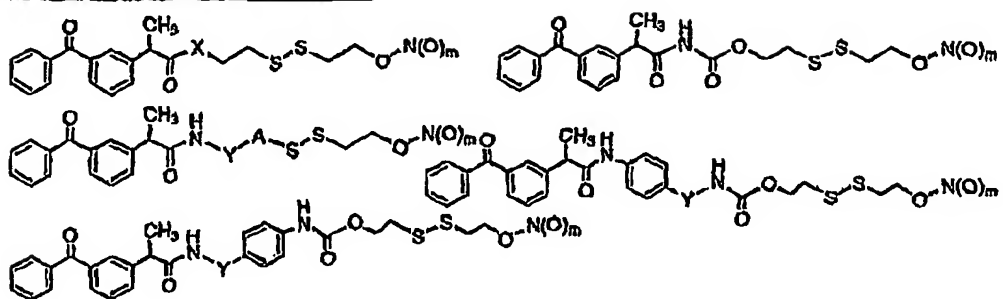
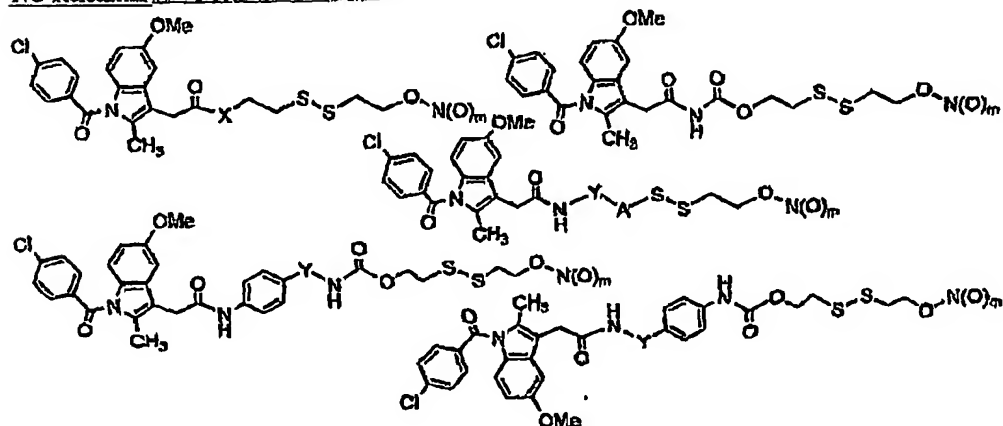
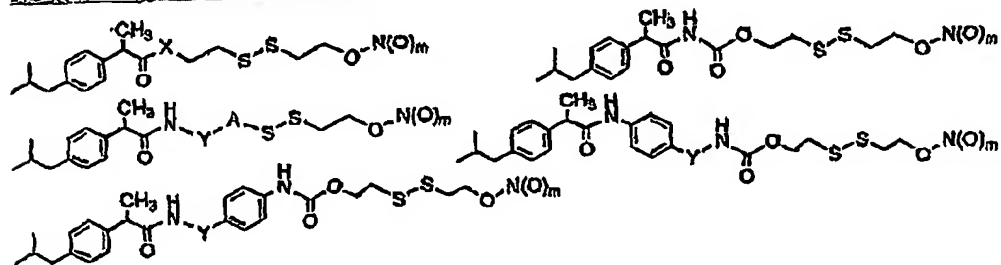


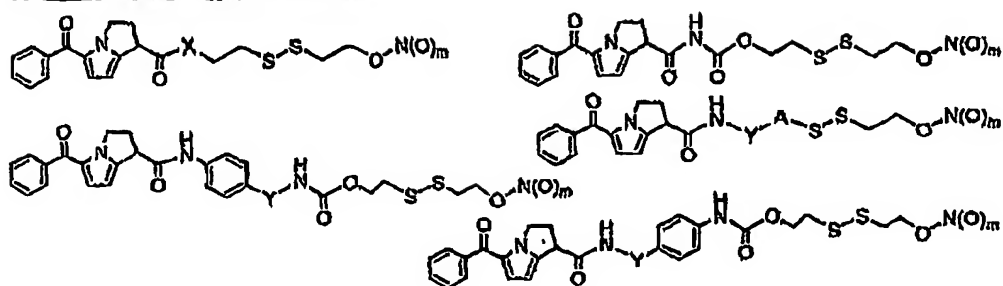
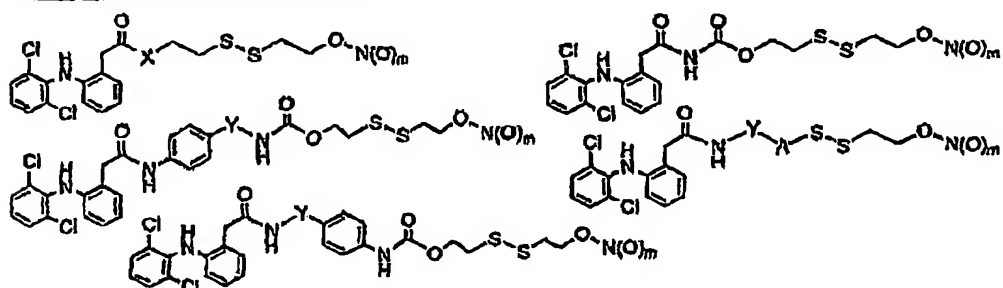
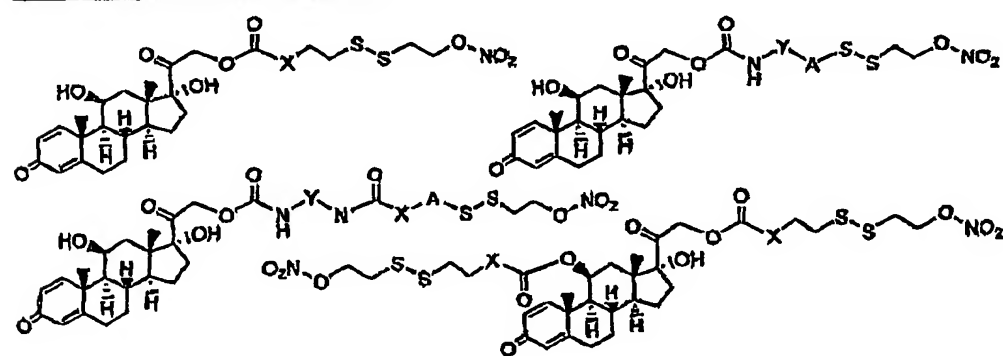
ADDITIONAL POTENTIAL EXAMPLES:

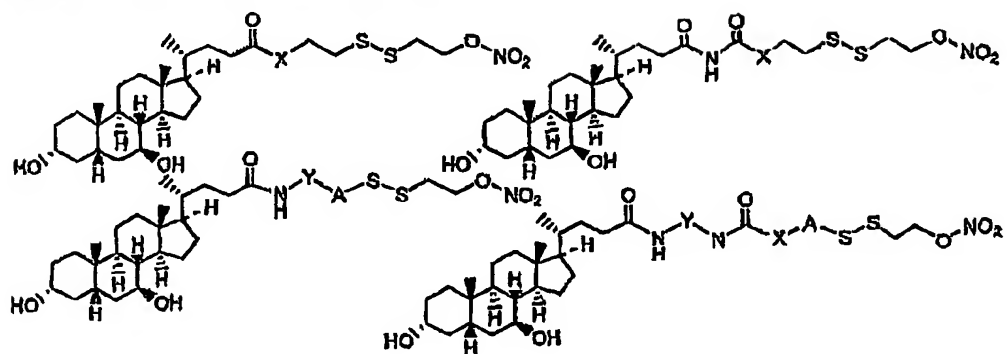
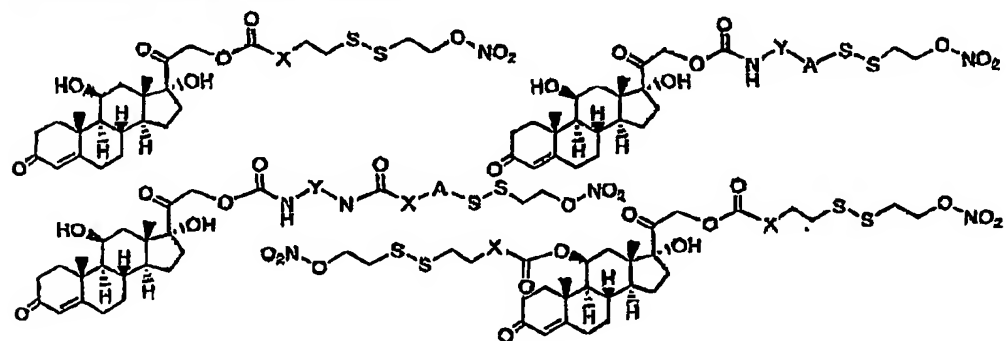
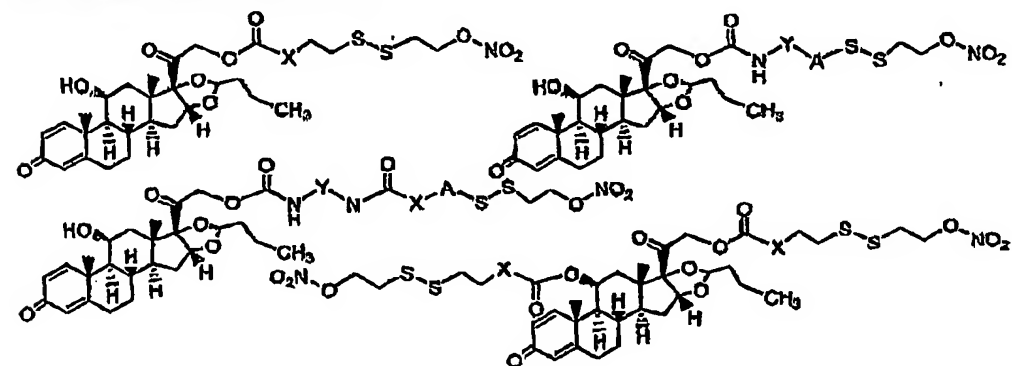
In the following additional potential examples, X is O, NR¹ (R¹= H, alkyl) or a bond; Y is CO, SO₂, P(=O)XR¹ or bond; R¹ is H, alkyl, aralkyl, or a metal ion; A is a bond, 1,4-/1,3-/1,2-phenylene or (CH₂)_o (o = 0-6) and m is 1-2 unless otherwise stated;

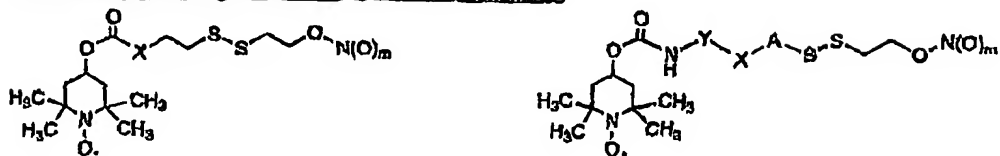
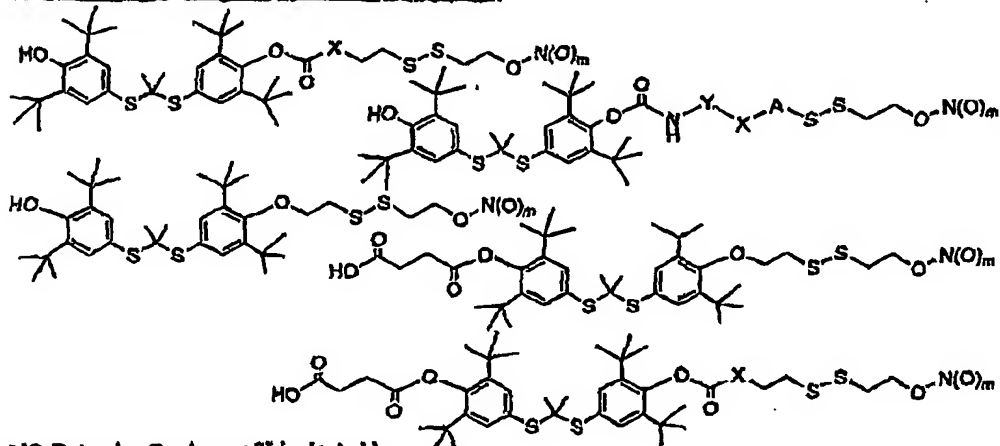
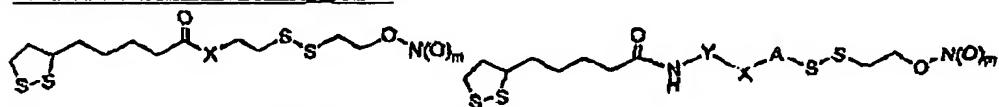
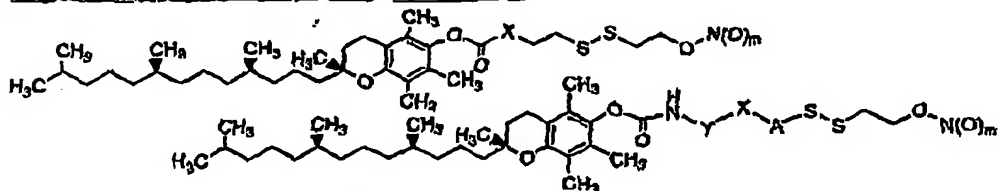
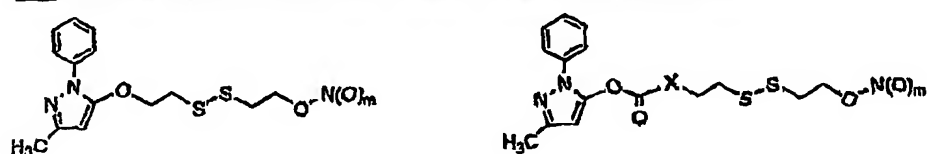
NO-Releasing Prodrugs of Nicotinamide:**NO-Releasing Prodrugs of NSAIDs:****NO-Releasing Prodrugs of Aspirin****NO-Releasing Prodrugs of Paracetamol****NO-Releasing Prodrugs of Meclizine**

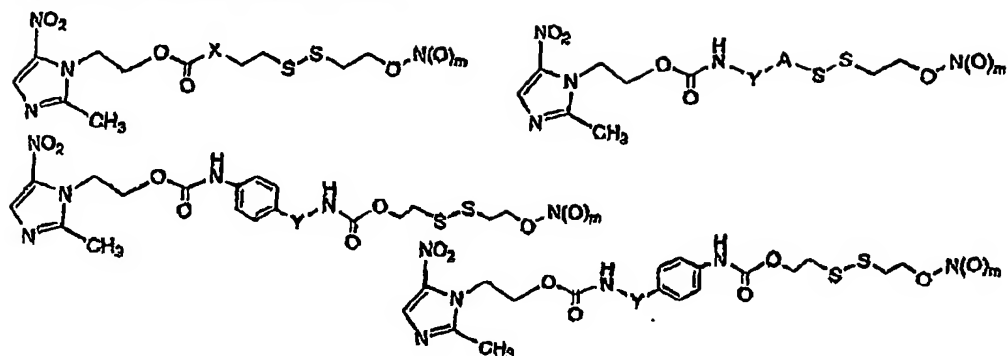
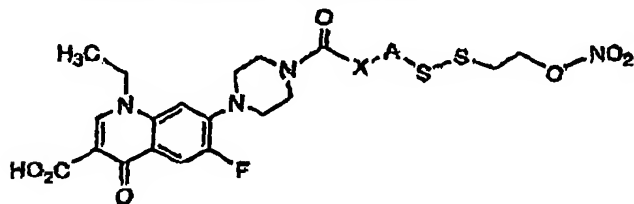
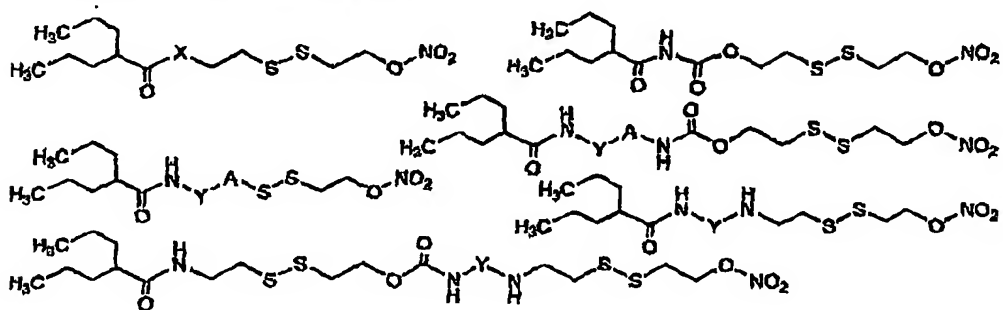
NO-Releasing Prodrugs of NaproxenNO-Releasing Prodrugs of FlurbiprofenNO-Releasing Prodrugs of Sulindac

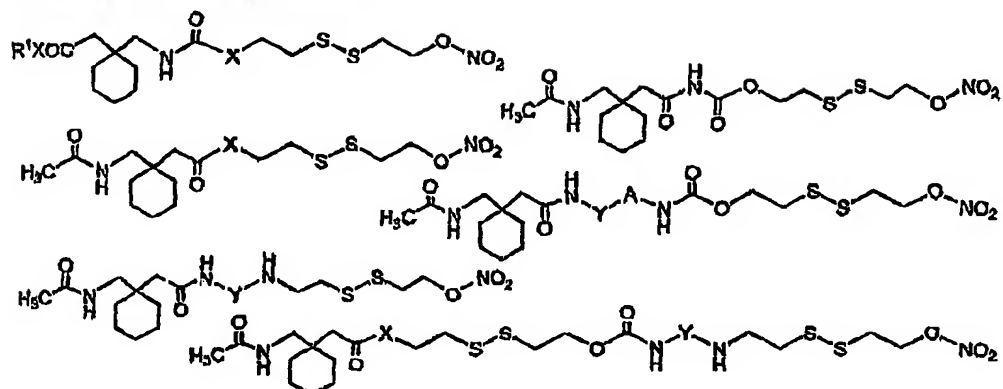
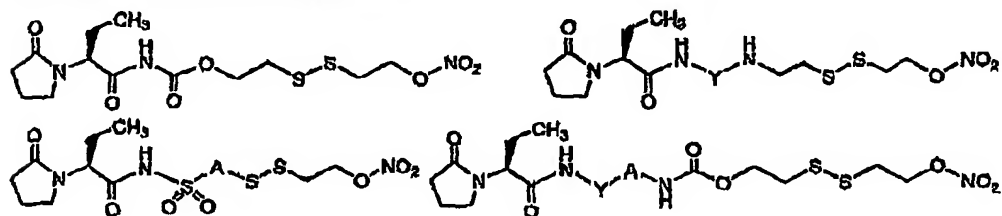
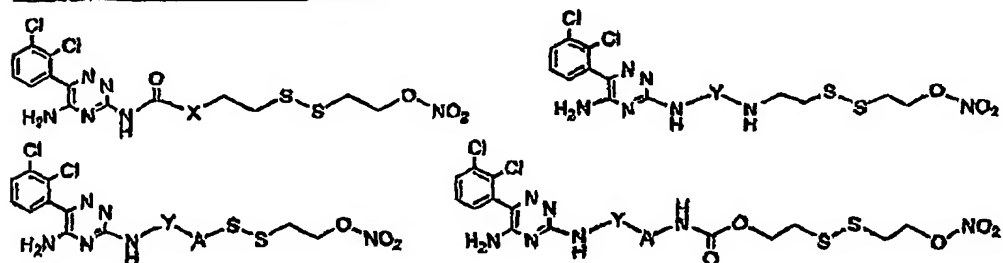
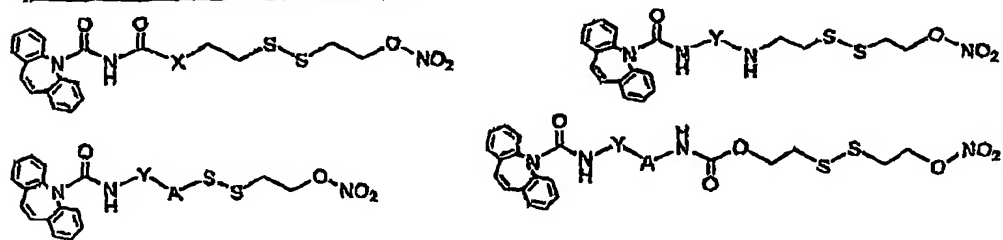
NO-Releasing Prodrugs of KetoprofenNO-Releasing Prodrugs of IndomethacinNO-Releasing Prodrugs of Ibuprofen

NO-Releasing Prodrugs of KetorolacNO-Releasing Prodrugs of DiclofenacNO-Releasing Prodrugs of Glucocorticoids:NO-Releasing Prodrug of Prednisolone

NO-Releasing Prodrug of Ursodeoxycholic AcidNO-Releasing Prodrug of HydrocortisoneNO-Releasing Prodrug of Budesonide

NO-Releasing Prodrugs of Antioxidants and /or Free Radical Scavengers:**NO-Releasing Prodrug of TEMPOL (4-hydroxy-TEMPO):****NO-Releasing Prodrugs of Probucol and AGI-1067:****NO-Releasing Prodrugs of Linolic Acid:****NO-Releasing Prodrugs of Vitamin E (alpha-tocopherol):****NO-Releasing Prodrugs of Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one):**

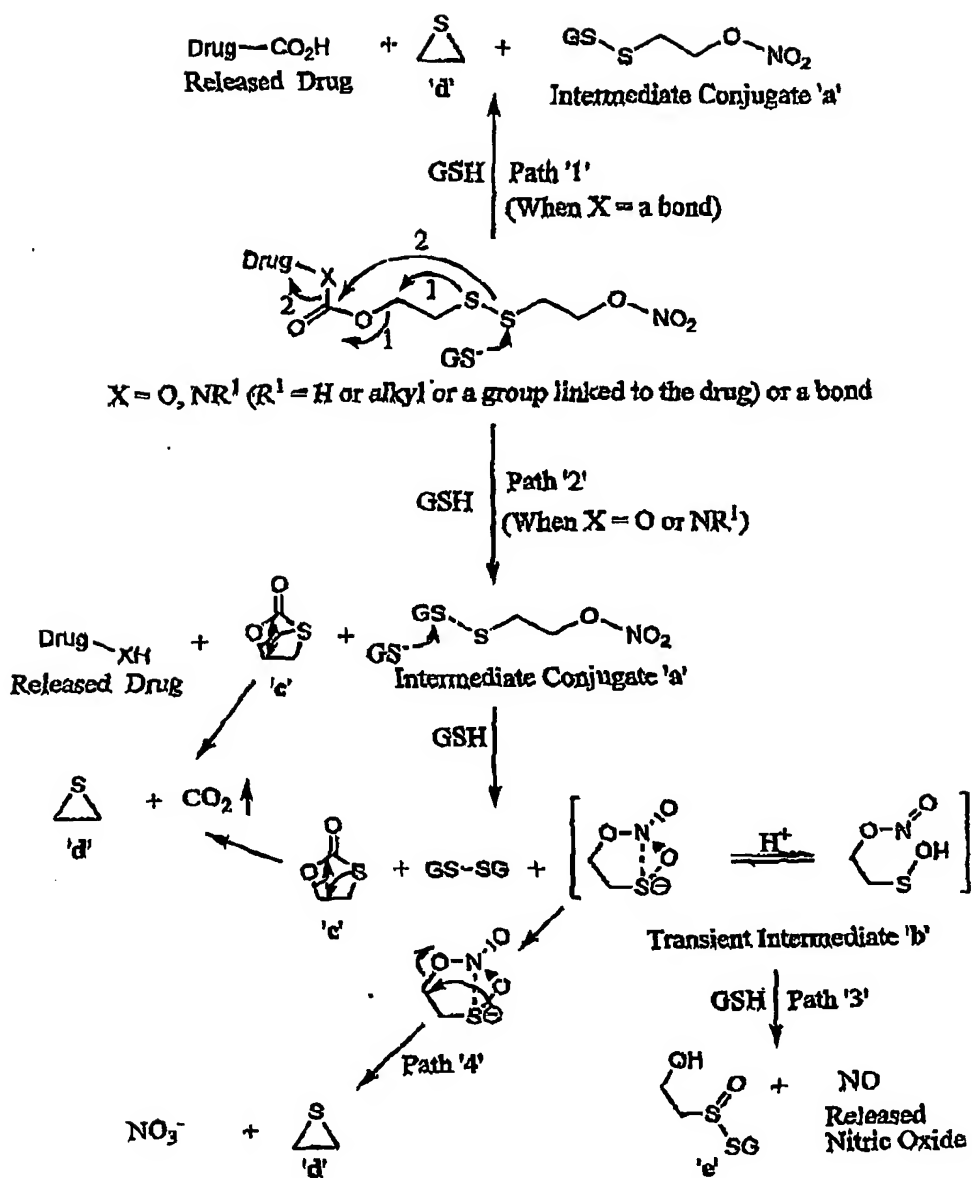
NO-Releasing Prodrugs of Antibiotics:**NO-Releasing Prodrugs of Metronidazole****NO-Releasing Prodrugs of Norfloxacin:****NO-Releasing Prodrugs of Antiepileptic Agents:****NO-Releasing Prodrugs of Valproic Acid**

NO-Releasing Prodrug of GabapentinNO-Releasing Prodrug of LevotiracetamNO-Releasing Prodrug of LamotrigineNO-Releasing Prodrug of Carbamazepine

6. Mechanisms of Drug Release from Prodrugs

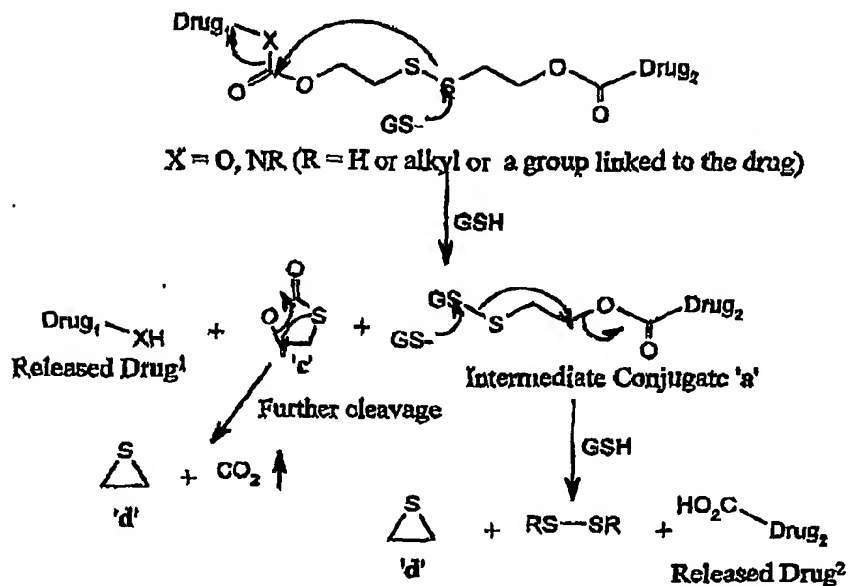
Drugs can be released from the prodrugs and mutual prodrugs via cleavage of bio-labile linker(s) in vivo (cleavage can be either chemical or enzymatic or both) by illustrative mechanisms as shown in Schemes M1 through M5.

- 5 Plausible mechanisms for concomitant release of nitric oxide (NO) and free drug from NO-releasing prodrug of amino-, hydroxyl-, or carbonyl-containing drug(s) are illustratively shown in Scheme M1. Thus, the attack of thiocyanate ion (from GSH or any other sulfhydryl-containing species) on nitrooxy-containing prodrug would release carboxylic acid-containing free drug, episulfide (d) and the intermediate conjugate (a)
- 10 according to path 1. If the prodrugs are made from amino-, or hydroxyl-containing drugs, then the prodrug would be cleaved via path 2 to release the corresponding free drug, the cyclic thiocarbonate intermediate (c) and the intermediate conjugate (a). The cyclic thiocarbonate intermediate may further breakdown into episulfide (d) and carbon dioxide. The reactive episulfide (fl) would be further neutralized by glutathione. The nitrate ester-
- 15 containing intermediate conjugate can further break down in the presence of GSH to glutathione dimer (GS-GS) and transient intermediate ϕ which can break down via path 3 to release NO. It is also possible that the same transient intermediate can break down via path 4 to yield episulfide (d) and a relatively innocuous nitrate anion (NO_3^-).



Scheme M1

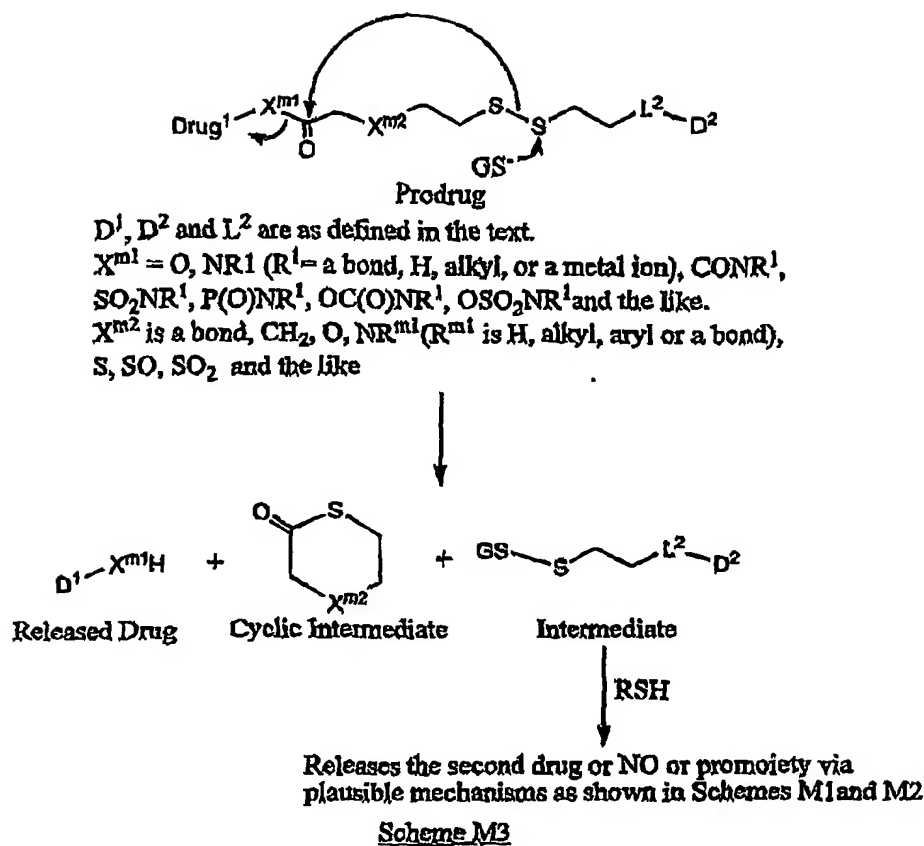
Plausible mechanisms of drug release from mutual prodrugs of one carboxyl-containing and one β -hydroxyl-containing drug is shown in Scheme JMZ



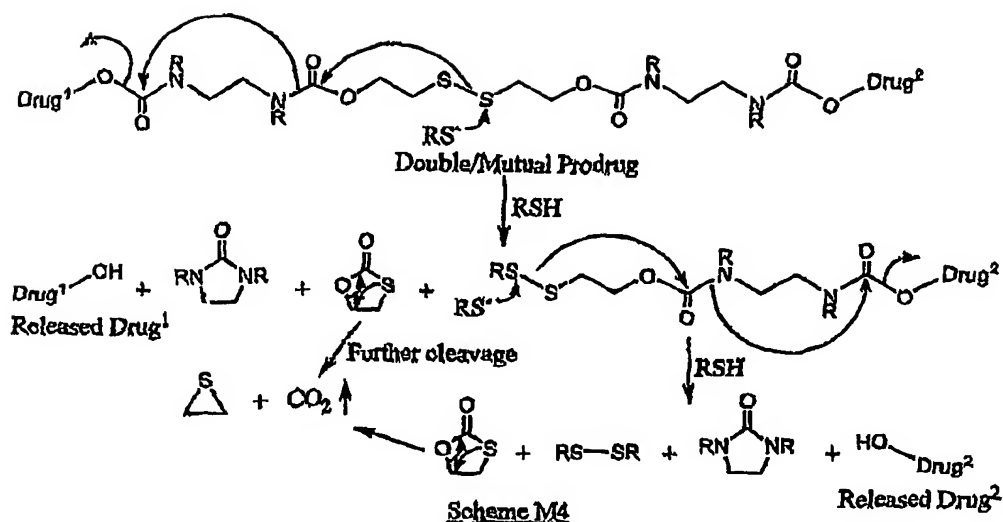
5

Plausible mechanism of drug release from prodrugs (including mutual and NO-releasing prodrugs of amino-, hydroxyl- and carbocyl-containing drugs) containing modified bio-labile linkers is shown in Scheme M3. Thus, the thiolate anion derived from the attack of glutathione on disulfide of the prodrug may trigger cyclization to release the free drug (DI-X-H) and a stable six-membered (or five-membered, if X is a bond) thioactone intermediate.

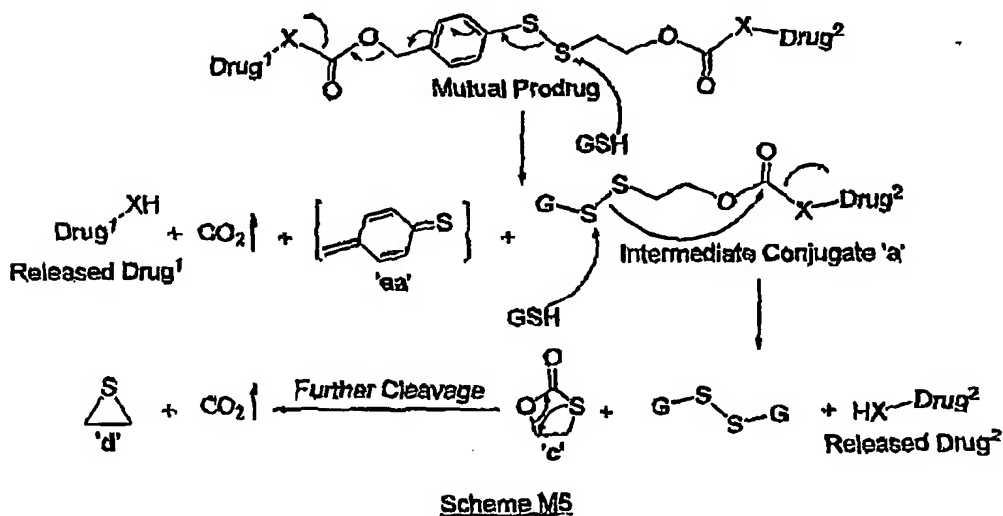
10



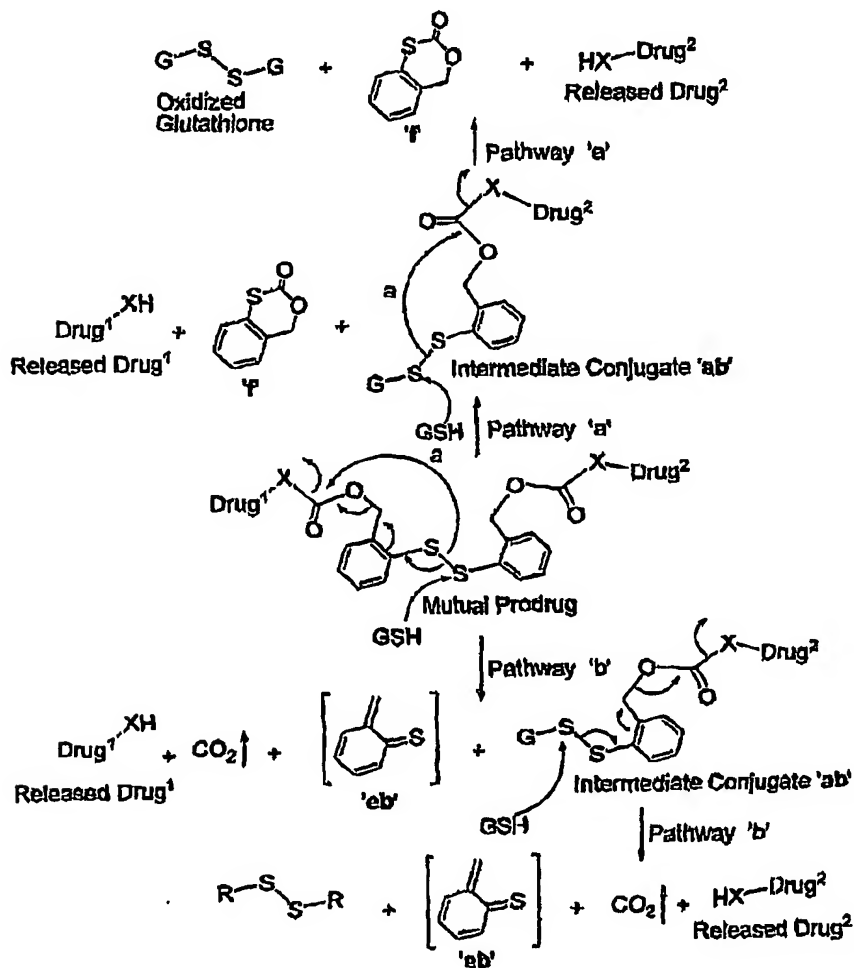
- Plausible mechanisms of drug release from, double/mutual prodrugs containing additional linkages to couple two hydroxyl-containing drugs are shown in Scheme M4. Thus, the thiolate anion generated by the attack of glutathione on disulfide bond of the prodrug triggers further cleavage as shown to release the free drug ($p\text{'-OH}$) and a substituted 2-imidazolidone. Through in vitro decomposition studies, we have found that the drug release from this type of prodrug is more facile when R group is an alkyl group,



This invention also covers novel faio-labilβ linkers containing 2,4-phβayleπe group and I₂-phenylene gtoiφ as shown in Schemes S and 6, irespectively. As depicted in Scheme M5, the linker is *expected to release* the free Drug¹ upon glutathione-assisted cleavage and may generate 1,4-qtrinonemetliϕid (ea) as a byproduct via 1,6-climirϕtjon process. Similarly, the free Drug² is expected to be released from the intermediate conjugate (a) as shovrϕ ïiti^je scheme.

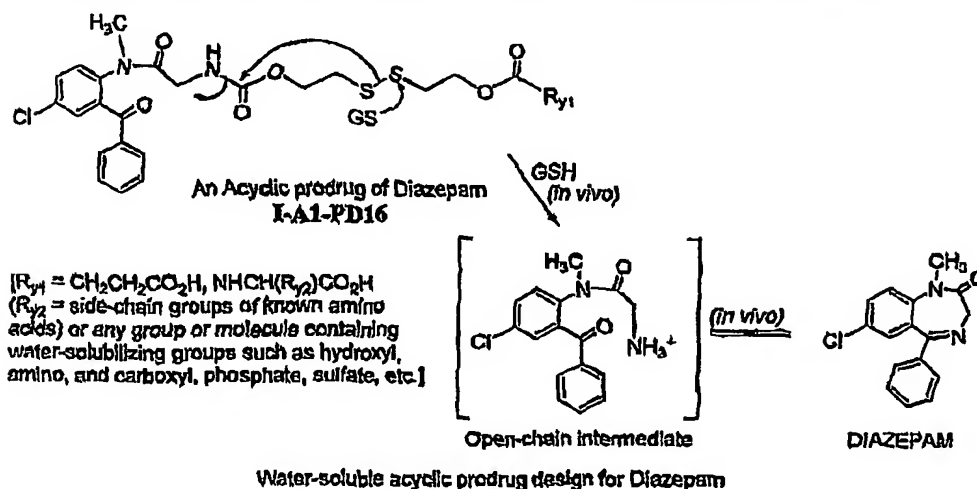


- As depicted in Scheme M#, the 1,2-phenylene-containing linker is also expected to release free drugs upon glutathione assisted cleavage and generate 1,2-quinonemethide (eb) as a byproduct -via 1,4-elimination process (via pathway V). However, this linker can also cleave via pathway 'a' to generate benzo-monothiocarbonate as a byproduct
- 5 Although the generated byproducts seem to be toxic, they are likely to be quickly neutralized by detoxification enzymes in the body.



Scheme M6

Scheme M7: Plausible mechanism of diazepam formation from an acyclic prodrug of diazepam



5 Diazepam, a benzodiazepine tranquilizer, is a very sparingly water-soluble drug and a water-soluble acyclic prodrug of diazepam can be made by using our linker technology. As shown in the Scheme M7, reduction of disulfide bond in the prodrug triggers release of open-chain intermediate of diazepam which spontaneously cyclizes to diazepam *in vivo*.

10 Where GSH is glutathione (reduced) or any other *in vivo* bioreductive agent that can reduce the disulfide bond. As illustrated, cleavage of disulfide bond triggers further breakage of the remaining portion of the linker to release the free drugs. In the process, some byproducts are generated and these are either eliminated or further degraded by some biological process. For clarity, the mechanism of cleavage of the linker is shown as occurring in stepwise manner. However, the steps can possibly occur in a concomitant fashion to release both the drugs simultaneously.

15 As illustrated in Scheme M3 and M4, Linkers may have additional spacer groups between one side (or both sides) of the linkers and the drug molecule and some of these spacer groups may be cleaved independently by a chemical or enzymatic process to release the drugs prematurely before the cleavage of disulfide linkage. The prodrugs and

mutual prodrugs containing such spacer groups may be useful when faster release of dm_g(s) is desired.

LISTS OF CANDIDATE DRUGS USEFUL FOR PRODRUG SYNTHESIS:

Drugs listed in the following list can be converted to prodrugs of formula I. This list is in no way limiting the scope of drugs covered in this invention, but given as representative examples. All the amino-, amide-NH, sulfonamide-NH, carbamate-NH, sulfamate-NH, hydrazone-NH, thiocarbonyl-NH, thioamide-NH, urea-NH, phosphoramidate-NH and the like. See above, for the description of "amino-containing drugs"), carboxyl-, hydroxyl-, oxime-OH), and catfjonyl (both aldehyde and keto groups) containing drugs under various therapeutic categories as listed in Merck Index (13th editions) and other data bases such as pubmed's Pubmed, integrity, and the like and also all the qualified (i.e., amino-, and/or hydroxy-, and/or carboxyl and/or carbonyl-containing) investigational drugs as listed in databases such as Metck Index. (13th editions), iddb, ensemble, integrity and the like are covered under this invention without any limitation.

ANTI-INFLAMMATORY DRUGS:

Arano-contatøing (including Amide NH and Sulfonamide NH and Phosphomiide NH^ etc.): Ampiroxicani, Bucolome, Celecoxib, Difenpipmide, 20 Mofebutaz, Nimesulide, Pata, P-Ocoxib, pataamide, Piketoprofeji, Tali, Tcnidap, Teiofenajflrøtey and Valdcocciib.

Hydroxyl-coj Λ ii-ing: 21-Acetoxypregnct toløne, Alcloroetasoue- alfe-Bisabolol, Budesowdc, Deflazacort, Difloiasone, Desonide, Desoximetasone, Diffioxasone, DiJ Θ cortolone, Diŧ ρ prednate, Ditaw $\ddot{\text{I}}$, Flwazacort^ Fluocjaonide. Flwcoftin Butyl, 25 Flupred $_{\text{f}}$ idene Acetate^ Glucanietaci π , Haleinottide, Halobetasol Propionate, Halo $_{\text{m}}$ etasone, Halopredone Acetate, Ibuproxam, i Λ teprcdnol Etabonate $_{\text{f}}$ Mazip $\ddot{\text{I}}$ edone, Mo $_{\text{H}}$ etasone Fufoate, Oxyphenbutazon β Perisoxal, Rimexolone.

Hydrotol-, and Amino-containing (including Amide ICH and Sulphonamide KH and Phosphonide ISH, etc): Bufexatrac, Etofenamate, Fevicadinol, Ibuprofen, Isoxicam, Lornoxicam, Meloxicam, Oxametacin, Piroxicam, Tenoxicam.

Hydroxyl- and sulphhydryl-containing: Tixocortol.

Carboxyl- and Amino-containing amide NH and sulphonamide NH

-hydroxybutyric Acid, Carprofen, Diclofenac, Etodolac, Flufenaric Acid, Meclofenamic Acid, Mefenamic Acid, Mefenamic Acid, and Tolfenamic Acid.

5 Carbosyl-containing: Acetnetacin, Acetamidocaptoic Add, Bemdazac, Benoxaprofen, Bettmoprofca, Bucloxic Acid, Butibirfen, Cimnetacra, Clidanac, Clopitac, Feibinac^ Fenbiiien, Fenolozic Acid, Fenoprofen, Fe»tjazac, Flurøxaprofea, ï lÖbjiprofea, Ibiipwfen, Indomeflia,cin, feofezoko, Iscrøþpac, Ketopiofen, Lonazolac, Loxoprofen, Metia^iide Acjd, Mofezolac, Naproxen, Oxapfozin, Pirazolac ^ Pirðrofcn 3, Pranopiofeii, 10 Protizi πc AcJd, Sulindac, Suprofen, Suxibtizon ß Tiaprofenic Acid, Tolraetin, and Tropesin.

Carboxyl- and Hydrosyl-containing: Balsalazide[^] Ettoxolonfe, Fβndosal,
Olsalazitie[^] Oxaceprol. and Ximoproferu

Amino-, Carboxyl- and Hydroxyl-containing: 3-Amino-4-hydroxybutyric Acid,
15 Mesalamine, and Sulfasalazine,

Keto-contaimtig: N-ibumctoae, and Piketoproftn.

Carboxyl- and keto-coistiamug; Bermoprofen, Bucloxic Acid, Igoxepac, Ketopiofen_π, Loxoprof_α, and Zaltiof_{βiv}

ANALGESIC AND/OR ANTIPYRETIC DRUGS:

20 Atnino-contaiftiog: AminocMoiitheitioXarf^ Aminopropylo π Aniloddine,
Antxfffenio,e, Benorylate^ Bβnpipetylofl, p-Btomoacetanilide, Butace(ω), Carsalam,
Difenamizolt, Etersalate* Ethcnzamidc, Ethoxazeoe, Flipirtiac Isodixin, Nifenazone,
Phenacetin, Pfoβnazopyridioe, Phenocoll, Phenopyrazone, Pianinodine,, Piiitramid^
' Picopacetamol, RattúfenazOfβ Pipetylone, Salveirinβ and Tinoridine.

25 Hydroxyl-coitaline, Aluminium bis(acetylsalicylate), Benzylmorphine,
Buprenorphine, Butorphanol, Chlorbutanol, Clorazepate, Codeine, Desomorphine,
Dihydrocodeine, Dihydromorphone, Dihydroxyaluminum acetylsalicylate,
Dimethylheptanoate, Ethanol, Ethylmorphine, Euglycine, Hydroxypethidine, Levamisole,
Meptazinol, Metoclopramide, Morphine, Nalbuphine, Pentazocine, Phenazocine,
30 Phenoperidine, Phenytoin, Salicylic acid, Tramadol, and Valproic acid

Carboxycyclo-octatinixig; Acetylsalicylsalicylic acid, Alclfenac, Aspirin, Benoxaprofen, 5-Bromosalicylic acid acetate, Ciqchophen, Diacerein, Dipyracetyl, Fosfosal, Ibufaiiac, Moprofen, and Salicysulfhric acid.

Ataino- and Hydra ϕ l-eontaijljtøg: Acetaminophen, Acetaminosalol, Bueetin,
 5 Capsaicins, Pezociae, Floctaceniifø Glafenine, Jsoiadol, p-LacfophenetJde^
 · Norievo ϕ hanol, No π urphi oø, PhenyltrainidDĪ, Salacetamictæ, and SaKcylaraide.

Amino- and Carboxyl-containing: Actarit, Buniflodizone, Cloxacillin, and Salicylamide O-acetic acid.

Carboxyl- and Hydroxyi-containing: DiflusaJ, Gentisic acid, and Salsaiate.
10 Keto-oojitaining: Atntolraietin, DipipancA, Hydrocodone, Isomethadone,
Methadone, Koipipane, and PheOdoxone.

Hydroxy- and Kato-containing; Hydromorphone, Ketobemidome, Metopon, Oxycodone, ajttb Oxyxnoiphone.

Carbonyl- and Keto-containing: Clometacin, Ketorolac, and Zomepirac.
15 Amino- Carboxyl- and Keto-containing: Bromfenac.

ANTIHYPERTENSIVE DRUGS:

Amino-containing; Alfbozin, Benzylhydrochlorothiazide, Bethesda M
Bopmdolol; Budralazin B Bunazosin, Ciclosidomine, Clonidine, Clopamide,
Cyclopenthiazide, Dehriosoqui, Ed^erpidine, Diazoxide, Dihydralzam B Doxazosin,
20 Eudmla Sne, Guanabenz, Guanaclic, Gwanazodiae, Guanethidin E, Guanochlor,
Guanadiel, Guaoflitte, Guanoxa T, Hydracarbrone, Hydralazine, Hydrofloroethiazide,
-hdapaaide, Itojranwi, Irbesartan, Ketanserin 5 Lofexidine, Mebutamate,
Mecamylamine^ Methyl 4-pridyl ketone thiosemicd wazone, Mib Bradil, Minoxid-l,
Monatepil, Moxonidine, phacipfazme, Pitacil, Piazosi T Raubasine, Resciiraamioe,
25 Reserp Üine, Reserpi Te, Rilmciidine, Syrossi Ogopine, Tasosaitan, Terazosin, Tiam Btidine,
Todtalazi Te. Tolo Tdke, Tripamide, ma Ürapidil.

Hydroxy-eontsjung: Ajmalin, Cicletan, Levcrorakaljm, Naftopidil, Phenactin, Optin, and Protoveratrine.

30 Catboxyl-containing: Epros-trtan, Fosinopřil, and Tetanisartaa,
 Amino- sŰl Carbosyl-containing: Al^cepril, gama-Aroinobutyric acid,
 Benfiepril, Caixdcartan, CaTŰnox,řle, Cawnapril, Cilazapřii, DelapřŰ, Enalapril,

Enalaprilat, Imidapril, Lisinopril, Moexipril, Moveltipril, Perindopril, Quinapril, Ramipril, Stasia, Spirapril, Teraocspil, Tandolapril, and Valsartan,

- Amino- *mi* Hydroxyl-containing: Acebutolol, AlprenoH, Amosulajol, Arotinolol, Atenolol, Betaxolol, Bisoprolol, Bosentan, Bucindolol, Bufeniode, Bunitrolol, 5 Bupranolol, Butofilolol, Cadralazine, C β Ziprolol, Carazolol, Carteolol, Cetamolol, Carvedilol, Epaolol, Indenolol, Nadolol, Dilevalol, Fenoldopam, Guanoxabenz, Labetalol, Losartan, Mepiudolol, Metipra π olol, Metoprolol, Moprolol, Nebivolol, Olmesartan, Oxpt β aoJol, Penbutolol, Phentolamine, Pildralazi π e, PMdiolol, Propranolol, Rescunetol, Sulfinalol, Talmolol, Tertatolol, Timolol, and Trimaz α in.

- 10 Aitiitto-, Hydroxyl- and Carboxyl-containing: MeUiyldopa, and Sampatrilat, SiilMydtyl-andCarboxyl-coit-uning; Captopril, andOmapatrilat, Carbonyl-containing; Araaidipine, and Epleireione,

ANTHBIOTICS:

- AU Hie known amino-, hydroxyl-, and carbosyl-containing antibiotics such as 15 Amoxicillin, AmpiciUin, Olivanic acid, Metronidazole, and the like; as listed in Merck Index. 13th edition and other drug databases integrity, ensemble, iddb, and ω c like. These antibiotics can be used in combination with beta-lactamase inhibitor such as clavulanic acid, penicilUinic acid sulfone and the like. The following lists of antibacterial and antifungal agents are given for clarity.

20 ANTIBACTERIAL AGENTS*

- Amino-containing: Ac β lapson, Acetosulfon β sodium, Ambazon, Bacampicillia, Benzylsulfamide, Brodimoprim, Cefcapene p β voxil, Cef ϕ odoxime ptoxitel, Chloramphenicol, Cilofam π e-T, Capromycin, Clofazimine, Cycloheximide, Cycloserine, D β soae, Ethionamide, Furazolidone, Moride \wedge N2-Fo π nylsulfison \ll dine, Puronamide \wedge Isoniazid, 25 Lenampicilli β LmezoHde, Mafeoide, \wedge -(\wedge \wedge lwlfamoylJsulfanilaniKcie, Mol β haza \ll amtde, Nlturadene, Nitrofurantoin, Penamcillin, Penethatnate hydriodide, Pexiganan, Pivampicillin, Pivocfalex β , Pidoxydine, protionamide \wedge Pyxazinamide, Solasulfone, Subathii ω α , 4,4'-Sulfinyldiamli π \wedge Sulfoxone sodium, 4'-Sulfanilylsulfanilaride, Sulfo π azide, Sulfabenzamide β Sulfacetamide, 30 Sulfaciloipy π dazine, Sulfecytia β Sulfediazine, Sulfadiazine, Sulfadim β roxine, Sulfadoxone, Sulfethidole, Sulfaguanidine β Sulfaguanide, Sulfetene, Sulfamethoxazole,

Carboxyl-containing (includes sulfate and phosphate-containing) !
Aminocyclitol, Aminoglycoside, Fluoroquinolone, Fosfomycin, and Hydroxamate add.

15 Azlocillin, Azheo_fam, BaciUacin, Balofloxacin, Betaraipron, CaⁱbröcilHn,
Caⁱnda_cillin, Carumonam, Ceföcloj, Ceñzcdone, Cefazolz, CetfiaWta, Cefdioren,
Cefepime, Cefetamet Cefixime, CefineuoXíme, Cefiaetezole, CefOdiam^B, Ceforanide,
Cefotaxime, CdFotßan, Ccfotiam, Cefoxitin, Cßrozopran, Ceφitnizole, Cefpkome,
Ceβoxadine, CeModin, Cftaaaidiroe, Cfteram, Cftezole, Ceftibnten, Ceftioxime,

20 CefttiaKongβ, Cefoioxime, Cefitzonam, Cephaçtilßsodimπ, Cephal«d τ Cephaloglycto,
Ceph_aloridinc Cephalosporin C, Gephylothin, Cephapitin so^djiao, Cephmdinc,
CUastatin, Cip_oflaxacm, Clmafloxacm, ClometocOBn, Cyclacilto, Didoxacillm,
E_f oxacin, Epicillm, F^b ðncilliπ, HoxadUto, HetecUIH Loracarbef, Metampidlⁱn,
MethioUK MezlociUi., NafcUltn, NopiysOlsemide, Opimizide, Oxacf c PeπciHmCs),

25 Penimepicyclme, Phe_{ti}ethicUI^ phthalylsulfecetomide, Phthalylsulfethiazole,
Piperacillio, PröpicilHn, Qua** SuccinylSulfaUdazole, Succjsulfone, Sulbenicillm,
Sulfechtysoidine, Sulfenilic acid, Temocilliα Ticateilliπ and Tigemonam.

96

- Doxycycline, Enviomycin, Ethambutol, Formicjas, Genteroyco Olyconiazide, N4-beta-D-Glucosylsulfa π latnid β , Gra_nicidm(s) $_3$ Isepamicin, Karamycin (ζ), Lkcomycin, Mectocyclone, Methacycline, Micronoidm, Neomycin, Netilmicin, Novobiocin, Paromomycin, Phenyl aminosalicylate, Pipacycline, Polymyxin, Primycin, Ramoplanin*,
- 5 Ribostainycin, Rifabutin, Rifalazil, Rifamidine, Kifamycin SV $_3$ Riampin, Rifapentine, Rifaximin, Ristocin, Salina2id $_7$ Smacycline, Sisomicin, Streptolydigin, Streptomycin, Streptotetrazole, 2-p-Sulfamylalajilinoethanol, Thiamphenicol, Thiostrepton, Tobramycin, Tuberactinomycin, Vioracyclin, and Virgimamycin,
- 10 Hydroxyl- and Carboxyl-containing (including sulfate, phosphate and phosphonate-containing): Fropenem, Nadifloxacin, Biapenem, Fusidic acid, and Merbromin.
- Hydroxyl- and Aldehyde-containing: Josamycin, Leucomycins, Midecamycins, Miokamycin, Rokitamycin, and Spicamycin.
- 15 Amphotericin $_3$ Hydroxyl-, and Carbon-containing (including sulfate, phosphate and phosphonate-containing): p-Aminosalicylic acid, Apjoycline, Aatiflicillin, Apalcillin, Aspicillin-t $_j$ BzoylpaS $_j$ Cefadroxil, Cefemandle, Cefatrizine, Cefbuparone, Cefdinir, Cefinone, Cefonicid, Cefoperazone, Cefosdis, Ceftriaxone, Cephazone, Eriactem, Flomoxef, Imipenem, Lincycline, Meropenem, Moxalactam, Nigamycin, Panipenem, Ritipenem, Salazosulfadimidine, Sulfolone acid, 4-Sulfamylalajilinoethanol, Teicoplanin, Tyrocidine, and Vancomycin.
- 20 Keto-containing: Tioleandomycin.
- Hydroxy- and Keto-containing: Carbomycin, Clarithromycin, Erythromycin, erythromycin ester derivatives, Oleandomycin, and Telithromycin.
- Hydroxy-, Aldehyde-, and Keto-containing: Rosaramicin.
- 25 Amino- and Keto-containing: Porfomycin-
- Carboxyl- and Keto-containing: Fleroxacin, Flumequine, Miloxacin, Nalidixic acid, Ofloxacin, Oxolinic acid, Pefloxacin, Piromidic acid, Ptilofloxacin, Rosoxacin, and Rvloxacin.
- Amino-, hydroxy- and Keto-containing: Cblordtracycline, Dalacin, Guamecyclone, Mikamycin, Minocycline, Oxytetracycline, Piistinamycin, Quinupristin, Rolitetracycline, Spectinomycin, and Tfospectomycin.
- 30

Amino-, carboxyl*, and Jketo-containing: Gaienojactø, Gatifloxaoin, Gcmifloxacio, Orepafloracia, Lotnefl Økadn, Moxifloxacin, Norfloxacin, Pazuiloxacin, Pipcmidio acjd, Sitafloracin, Sparfloracin, Tosufloxacjo, and.Trovafloracin.

Sulfehydryl-cottaining; Pjrithiotte.

5

ANTIFUNGAL AGENTS:

Attiino-containing: Chlordantoi π, Exalamid β Flucytosine, Loflucarba Λ Magenta I₅ and Pyrolnit)dn.

Hydroxy-coitaining; Cblorpliiβesi π, Cid,op li»3i,, Dermoatatin, Filipin, 10 Fhicomazole, FuΛgichroffito, Pecilocin., Posac Ohazole, Ravuconazole, Rubijervine, Siccac Ún, 2,4,6-Ttibromo-TO-ctesol and Voriconazole,

Cíffboxyl-iititeúúig: Undecyleaic acid (KMffidecenoic acid), and Propionic acid.

Amino- and Carboxyl-contain Ógt Azaserine,

AñO'mo- and Hydroxyl-containing: Salicylaailide, AciiSorciDi (9-Aminoactindine 15 coiøpoufld with 4-Hexylresoroinol (1:1)), Anidulafungin, Bromosalicylchloianilide, Bnclosamide, Caspofangin, Micafimgin, and Tubercidin.

Aroiπo-, CaΛoxyl- and Hydroxyl-contain Íng: Natamycin, Amphotericin B, Lrøensomyia, and Nystatin.

Carboityl-coutaiiing: sodinm propionate and griseof Øvia.

Hydroxy- and carbonyl-contai^ing: Vitidin. 20

Amino-, hydroxyl-, aØ carbonyl-contauraig: Peπmycin and MeSpardc«x.

Amino-, cwboxyl-, hydroxy!-, and carbonyl-containiBgt Candididin.

ANITVIRAL PRUGS:

Hyd Íoxy-containing: Edojtudine, Floxutidine., Idoximidine, Kethoxal Λ 25 Pod Øphyllotoxin, Sorivtidroe, Stavuduie, Triflmidine, and Zidovudine.

Amino-c Øntai πng: Amantadine, Afflidinoiyncjn, Atevirdin β Capravuing, Delavirdinc, Efavirenz, Famciclovir, toaquimod^ Lamivudiiæj Methisazone, MoioTcydine, Nevimpine,, Osetamivir, Rimantadine, Stallimycin^ roantadme, and Valacyclovir.

Amino- and Hydroxyl-comaining: Abacavir, AftyedØvir, Adefovits, AmF ei«v fr> 30 Atazanavir, Cidofovir. ÍMdanosine, Didc Øsya Óenosfene, Emt Ócitabiae, Entecavir,

5 Amino-, Carboxyl- and Hydroxyl-containing: Zanamivir,

Amino-catalytic; Chlorguanide, Chloroquine, Chlorpioguanil, Cycloguanil, Pamaquine, Placidol, Primaquine, Quinocid and Tafenoquine.

Hydroxyl-contai π ng: Artemisini π alcohol, Bebeerineg, Cincljonidin β

Amino-, and Hydroxyl-containing: Amodiaquin, Hydroxychloroquine,
Mefloquine, and Pyronaridine.

Catbojoyl-contaitŵig: Arteflece,

[illegible]

Ammo-containing (including Araide-NH and Sclphojamide-NH, Carbamate-NH,

- oxo-L-aspartate (DON), Edatrexate, Eflornithine, Enitracil, Etoposide, Fluorouracil, Gefitinib, Gemtazabine, Goserelin, Histamine, Ifosfamide, Irinotecan, Imiprosulfan, Lanreotide, Leuprolide, Liarozole, Lobaplatin, Cisplatin, Carboplatin, Lomustine, Lofosfamide, Marimastat, Melphalan, Methotrexate, Methyl
- 5 Amiolevalinate, Miboplatin, Mitomycin, Mitoxantrone, Nilutamide, hTunustine, Nolatrexate, Oxaliplatin, Pemetrexate, Phetimet, Pmtrexone, Procarbazine, Raltitrexed, Tariq Umar, Temozolomide, Thiamiprine, Thioguanine, Tipifamib, Tirapazamine, 3-Aminopyridine-2-carboxaldehyde isosemicarbazone (3-AP)/ S-Aminopyridine-methyl-2-carboxaldehyde isosemicarbazone (3-AMP/Triapine /OCX491/OCX-0191) „
- 10 Trimetrexate, Uracil Mustard, Urethane ([Bis(1-aziridinyl)phosphoryl]acetic acid ethyl ester, ethyl carbamate and Methotrexate.

- Biohydroxy- & Amino- containing (including Azoxide-NM and Sulphonamide-NH₂ Carbamate-ISOH, Sulfonamide-BH, and Phosphorothioate-NH): Ancitabine, Anthracycline, Azacitidine, Bleomycins, Bupropion, Buserelin, Carbimide, Chlorzoxazone, Cladribine
- 15 Cytarabine, Daunorubicin, Decitabine, Defosmide, Docetaxel, Doxorubicin, Ectoparasiticide, Epirubicin, Gemtazabine, Hydroxyurea, Idarubicin, Marimastat, 6-Mercaptopurine, Pifostyline, Plomycin, pifostyline, Pirarubicin, Prinomastat, Purorocitin, Ranimustine, Streptozocin, Tiazofurin, Troloxibine, Vindesine and Zorubicin.

- 20 Carboxyl-containing; Butyric acid-

ANTIOXIDANTS/FREE RADICAL SCAVENGERS;

- Amino-containing (including some investigational drugs): B1X-51072 (4,4-dimethyl-3,4-dihydro-2H-1,2-bisphosphazene), Carnosine, Mdatom (+)-R-Piamipexide, and Stobadine.
- 25 Hydroxyl-containing (including some investigational drugs): Ascorbic acid, Cu-cumin, Dexanabinone, Edaravone, (-) Epigallocatechin gallate, Emoxipin, Hydroxytyrosol, Idebenone, Luteolin, Nicotinic acid, NZ-419, Oxyresveratrol, Probenecol (it is a probenecol prodrug such as AGI-1067 and AGI-1096), Quercetin, Reductase, Silybin, Tempol (4-Hydroxy-TEMPO), and α -Tocopherol (Vitamin E).
- 30 Carboxyl-containing (including some investigational drugs); N-Acetyl L-cysteine, Alpha-Lipoic acid, Rapaunellin, and Tetrahydro-lipoic

ArainoVHydroxyl-, and Carboxykcontainrag (including some investigational drugs): N-Acdyl earnosine, ^Carnitine, and SCMC-Lys (S-carboxyπethyi-L-cysteine Lysine salt H2O).

5 Amino- and Hydroxyl-containing (including some investigational drugs): BN-82451, and Zeatui.

BN ZODIAZEPINE TRANQUILIZERS AND HYPNOTICS:

Diazepam, Triazolam, Alprazolam, and the like,

ANTIULCERAONENTS:

10 Anti-io-coπadñing (including Amide NH and Suñpfoojianiide NH and Phosptøtnide NH, etc): Aldioxa, Benexate HCl, Citøβtidine, Ebrotidke, Ecabapide, Esaprazoie, Eesomeprazolc, Famotidine, Ìrøogladitē, Laj&itjdine, Lansoprazole, Omepiazole, Pøfttoπazole, Pitcπziqjine, Pol^preïdnc, RabepressoK Ranitidine, RoKatidine, and Tfoxipida.

15 Hydroxyl (and Keto a^d Keto and/or Carboxy]) -containing." EØprostil, Misoprostol* Omoprøstfl, Plautiotol, Bioprostil, Tramoprastit, and Qryzanol A.

Carboxyl-contaioing: Acetoxolone, Carbenoxolottβ Rebamipide^ and Sofalcone.

Amino (or Hydroxy.) - and Catboxyl-coftaitwng-' Cctrajeate, Ecabet, S-MetHylmethionin^ RosaprostoL and Rotraxate.

Carbonyl-contaaiing: Spj2ofiirone, and TepreπtoOe.

20 ANHCONVÜLSANTS;

Amino-contaitra β (including Amide NH and SØ bonamide NH aad Phosphoioid© NH, etc.)- Acetylphenet Øide, Albutoin, iV-benzyl-3-chloroπtopioπamide, Cayba,nazepine, Cinromidβ Clonazepam, Decimemidβ Dimethadione^ Doxcnitoin, Ethoauximide, Ethctoift, Felbamate, Fosplieiiytoin, Lamotrigine, LeveÜracctaiπ, 25 Mephcnitoin, Mephobarbital, MetñiarbiH MØhctoiπ, Nitrazepam, Oxcarcazepitøe, Qñ c&waxmzeπiÙe, Phenacewid β Phctoefljarbital, Fhenctoride, Phenobarbitad, Phenylmethylbaibituristic Acid, Phenytoro, Phethenylate Sodium, Primidone, Progabide, Remacemide, Rufinamide, Suølofenide, Sulñiiame, Talampanel, Tetrantoin, Tojrømate, Valpfomide, Zonisamide, 5-Methyl-5-(3-phenanifaiyl)hydaÜtoin, and 3-Methyl-5- 30 phenylhydantom.

Hydroxyl-contaimng: Ganaxoloie.

Hydroxyl-, and Amino-containing (including Amide NH and Sulphonamide NH and Phosphonide JSIH). 4-Amino-3-hydroxybutyric Acid, Atrolactamide, and Buramate.

Carboxyl- and Amide-Containing (with Amide NH and Sulphonamide NH and Phosphonamide NH): Gabapentin, Pregabalin, and Vigabatrin

5 Carboxyl-coπtaining; Tlagabiπe, and Valproic Acid,

ANTIPARKINSON'S: Levodopa & Carbidopa.

ANTIDEPRESSANT:

AmiOo-contaiTung (including AftÙde IsIH and Sulphonainide NH aod
Phosphomide NH₅ etc.): Amoxapine, CatoxaSiOpe, Deanejciptiline, Desipramme,
10 Duloxetine, Httoxetine, Fluvoxatine, Indalpine,, Indeloxazrae Hydrochloride,
İproclozide, Ipo niazid, Isocarboxazid, Levophacetopiane, Maprottinc, Metapramme,
Mitoaci Pran, Muiaptiue, Moclobemide, Nialamide, Nomifensine, Nortriptyline,
Octamoxi, Oxypetum, Paroxetine, Protøfylme, Reboxetine, RoKpram, Sßtmilin,
Tofenadn, Tfanykyp<>ni> Viloxazine, Bemoxtoe, and RÇicyprine.

15 Hydroxyl-contai π ung; Befloxatone, Bupropion, Fenpentadiol, Hypejicin, Opipramol, Pyrisuocideanol, Toloxaton β and Ventef-fl-ine.

Hydroxyl-, and Amino-containing (including Amide NH and Sulfonamide NH and Phosphonamide NH)? AdebysmctjioTune, 5-Hydroxytryptophan 9% and Roxidol β

Carboxyl- and Amino-Co-Claining (incliding Amide NH *m i* Sidphoaamfcfe NH
20 and PhoFphomide KH): AttMneptSne, and Tiatieptine,

ANTİHİSTAM İNtC

Atamoxifen (including Amide NH and Sulphonamide NH a α Phosphonide NH, etc.): Antazoline, Astemizole, Clobazepam, Desloratadine, Epinastine, Metronidazole, Mefenamic acid, and Triprolidine.

25 Hydroxyl-containing; Terfenadine, and T⁺Hydrox-yeihylpro π iethaane Chloride.

Hydroxy^α and Amifio-contaimng (Üichidfag Amide NH *m* α Sulphonamide NH and Plrøsph α ide WH, etc.): Cetoxim β

Carboxyl-containing; Acrtvastine, Bepota\$stine, Cetirizine, and Levocabastine,

Catboxyl- andHydroxyl-contai π ung: Fesofeiidaine.

ANTICANCER, ArøOxmA İTVB, ANTnNFLAMMATORY 5 AND
 CARDIOPROTECTIVE AGENT: Trans-Resveratrol [(EJ-S^^-tdhydrøjtystilbeoe),
 ANTIDIABETIC: Metformin, and Nategljjude/GHpizide/Glibenclajride (ß lybmiás).

5 It should be understood that while the lists of *names* of various categories of drugs
 have been included above, such lists \$ra presented in a way of illustration of the structural
 features of the qualifying drugs in this invention and therefore, the number and types of
 listed drugs are not necessarily limited; thereto. In principal, any amino-, and /or carboxy],
 and/or carbonyl-, and/or hydroxyl-containing drug (from both lcnovm and irtvest.gatioi.al
 drugs), irrespective of its therapeutic category and their mechanism of action, as listed in
 10 drug databases such as Merck Index, prous science's ensemble, integrity, iddb, and the
 like, are generally covered within the true spirit and scope of toe present invention. For
 clarity, in addition to the above lists of drugs, any amino-, and/or carbosyl-, and/or
 carbonyl-, and/or hydfoxyl-contajning drugfs) (both *known*, tod investigational drugs)
 from the following therapeutic areas are covered without any limitation:

15 CENfTRAt NERVOUS SYSTEM: Sedatives, Hypnotics, Antidepressants,
 Antipsychotics and Antimonies, Analgesics & Antipyretics* Antimigraine agents,
 Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for
 dementia, Antiemtics, drugs for Vertigo, CNS Stimulants & activators.

20 EYE: Antiinfective eye preparations, Antiitaflairmatory and antiallergie
 preparations, antiglucoma drags and other preparations b cUtE eye diseases.

EAR, NOSE and OROPHARYNX: Drugs used aural, nasal and otopharyngeal
 preparation.

25^ CAFDIOVASCULAR SYSTEM; Antiattfcythcmic drugs, Antihypertensives
 (including alfa/bBta-bloccers, channel blockers^ ACE inhibitors, Angiotensin II receptor
 antagonists, diuretics, etc.), Antianginals (including nitrates, 'calcium channel blockers,
 etc.), Drugs for cardiac Mure and shock, Vasodilators, Coagulants, AnticoaguJmits,
 Thrombolytics and antiplatelet drugs.

RESPIRATORY SYSTEM: Respiratory stimulants. Antitussives, Expectorants,
 Mucolytics and Decongestants, Antihistamine agents, and antiasthmatics.

30 GASTRO INTESTINAL TRACT: Antiulcer and Antisecretory drugs (including
 H₂ receptor antagonists, Ptooa Pvanp İinMbitors, Prostaglandin analogues, etc.);,

Antacids, Antispasmodics and drugs modifying intestinal motility, Antidiarrhoeals (including antimotility and antimicrobial drugs) *mi* drugs acting on gall bladder.

5 GEMtO URINARY SYSTEM: Urinary autii π fectives, Diuretics, U π aary analgesics & antispasmodics, Ant $\pi\pi$ fective drugs acting on urethra and vagina, drugs acting on uterus. Drugs for prostatic hypertrophy (including alfa blockers and antiaadrogens), Drugs for erectile dysfunction, and Spermicidal & nonhom ω nal contratceptives.

10 SKIN: Emollients and Jsetatolytics, topical antiinfectiv β s, topical antifungals, topical parasiticidals, topical steroids, topical drugs for acne vulgaris, drugs for psoriasis, pigmentation disorders, and Antiscbotthoeics.

MUSCULOSKELETAL DISORDERS; Non Steroidal Anti Inflammatoiy Drugs (MSAIDs) including COX-2 inhibitor Aatiarflø itic agents, π mmunosuppressants, Topical analgesics, Muscle relaxants and Neuromuscular J>rags.

15 INFECTIONS AND INFESTATIONS: Penicillin antibiotics, CepHalosporin antibiotics, Quiuolone & Fluoroquinolone antibiotics, MacrolWe aoi β iotics, Ctøoramphenicol, Tetracycline antibiotics, Sulfonamides, Autiana ϕ otics such as Metronidazole, Antitubejcular drugs, AntUeprosly drugs, Antifimgats, Antiprotozoals, Anthelihitithics & Ant \ddot{U} nfestive Drugs, Antunalarials and Antivirals.

20 ENDOCaUNE SYSTEM: Anabolic and androgenic steroids, Corticosteroids, Oestrogens, Progestogens and Homional contraceptives, FettiUty Agents. Trophic fa. \ddot{o} lmones and related <frugs> Thyroid and antithyroid drugs, Antidiabetics and hyperglycaemics.

NUTIUXION: Vitamin^ Amino acids, Anti-obesity drugs

25 METABOLISM: Hypolipidaemic drags (including fibric acjld derivative^ statins [(i.e., HMG CoA ieductase inhibitois), nicotinIG acid group, β cj, Drags tised for Gout and Drugs affecting bone metabolism (including bisphosplxonates).

30 NEOPLASTIC BISOFDERS: Anticancer drugs such as alkylating agents, cytotoxic antibiotics, antimetabolites such as cytarbtae, Rudarbine, 5-Ftæoxo Uacil, Mercaptopurine, Thioguanine, etc., Vinca alkaloids and Etoposide, Taxancs, Topoisomeras β \ iid η bitors, Cytotoxic immunosupptessants, Immunostimtdants.

Cytoprotectives such as Ainfostine, Oestrogens, Progestogens, hormone antagonists and other antineoplastic drugs.

5 ALLERGY AND IMMUNOLOGY: Antiallergics such as non-sedative antihistamines (e.g., Cetirizine, Desloratadine, Terfenadine, Fexofenadine, etc.), sedative histamines and histamine receptor blockers.

ANAESTHETICS & SURGICALS: Local anaesthetics, intravenous anaesthetics, inhalation anaesthetics and muscle relaxants.

DRUG COMBINATIONS;

10 It is appreciated that prodrugs of any two or more drugs from the above lists of potential drugs can be used in combination depending on the medical application/need. While a combination formulation may occasionally consist of more than two drugs (depending on the medical need), the following pairs of drugs are covered in this invention as illustrative pairs of candidate drugs for combination therapy.

15 ANTICANCER: Paclitaxel and Doxorubicin, Paclitaxel and Mitomycin C; Paclitaxel and 9-aminocamptothecin, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-APy) 3-Aminopyridine-4-methyl-2-carboxaldehyde thiosemicarbazone (3-AMP) and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; CC-1065 and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; Trans-Resveratrol [(E)-

20 S^1 , S^2 -trihydroxystilbene] and another known anticancer drug such as Paclitaxel, Doxorubicin, Mitomycin C and the like; Renal acid (including all fatty acids) and Butyric acid. Paclitaxel and Captopril, Doxorubicin and Biotin. 5-Fluorouracil and Cytarabine. Edatrexate and Paclitaxel; Cephalosporanic acid and Paclitaxel; Cephalosporin and Paclitaxel; and Paclitaxel and Gemcitabine.

25 ANTIPARKINSON'S: Levodopa and Carbidopa.

ANTIBIOTICS: Amoxicillin and Clavulanic acid; Ampicillin and Clavulanic acid, Amoxicillin and Penicillinic acid sulfone; Ampicillin and Penicillinic acid, sulfone; OHvaleric acid (or any carbapenem antibiotic) and a renal dipeptidase (dehydropeptidase I) inhibitor such as 3-substituted 2-acyl-L-valine propionic acid and the like.

ANTILIPIDEMIC AND HYPERTENSION: LjflbwI and
 IL<va#ati-i/ī>ravasta^^ luvastatin/Atorvastatin/Simvastatin; Ezetimibe and Lovastati π
 Pravastatin/ Flwastatin/Atorvastatin/Siinvastat īπ

Amlodipme and Lovastatin/P*avastatii^luvastatii^Atorva^tijySimvastatut

5 ANTIDIABETIC: Metformin mā Nateglinide/Glipizide/GKbeiclamide
 (Glyburide)

ANTIDIABETIC AND HYPERTENSION: Metfbratift and
 Lovastati π/Pravasiatiti/Fluv.^tatin/Atorvastati-1/S imvastatin.

10 ANTI-ASTHMATIC, ALLERGIC RHINITIS AND CHRONIC OBSTRUCTIVE
 PULMONARY DISEASE (COPD); Psetidoephedtfne and
 Fexofenadine/Ce^mine/Deslotatadinc/Epinastine; Salbutamol and Ipratropium btojnide;
 Mometasone aod FQmoterol/Salmeterol; Fluticasone and Foπoterol/Salmcterol;
 Budesonide ad Foπotcrol/SalmetetoL

15 ANTIARTHR ITIS, INFLAMMATION AND ULCERS: Diclofenac (any known
 NSAID) and Misoprostol; Diclofenac (any knQvrø NSAID) aod a proton pump inhibitor
 su,cīx as Omeprazole, Lansoprazol, Rabepxasol β LramnQpraz Qe, Pantoprazole, and the
 like. A known antibacterial agent and a proton pump inhibitor such as Omeprazole,
 Lansoprazol, Rabeprazole, Leminoprazole, Pantopra2ola, and the like; Naproxen (or any
 known NSATD) and Prophenazone; Acetaminophen and
 20 chlorzoxazone/iaietaxalane/mepkenoxalone.

ANTIVIRAL (HIV/AIDS, HEPATITIS B AND OTHER VIRAL INFECTIONS):
 Zidovudine and Lamivucūhe-, Triple prodiug of Zidovudine; Lantfvudine and Abacavir
 (Ziageo,); topinavit and Ritonavir; Lanaivudine and Adefovir or its prodrug adafovir
 dipivojdl; Amprarøvj_r and Zidovudine; Nelfinavix m &a. nucleoside revefsβtranscriptase
 25 inhibitor such as Zidovudine L-anivudine, and the like; Stavudine and an anQetroviral
 agem such as Zidovudfaiβ Laπuvudin β and the like; Dideoxyino īine and m antiretrovital
 agent such as Zidovudine^ Lamiv Qli Qe, and the Jike; Eratricitabinc and
 Penciclovir/Faracidovit; Acyclovir (or any other kπovra antiviral compound) find a bite
 acid such as oholate, deoxycholate, chenodeoj Σcholata, and ursodeoxycholate <|S>J:
 30 targeting bile acid transporters for enhanced oral bioavailability of the drug; Triple
 prødπg of Zidovudine, kamivudme and EfaviterøΣ

5 In addition to the Above list of drugs, the present invention also covers newer drugs with the above mentioned active fractional groups as listed in the Merck index (13th edition) and other drug databases such as Prous Science's ensemble, integrity and the investigational drugs as listed in databases such as iddb, ensemble, integrity, and the like without any limitation.

10 It should be understood that either or both of any selected pair of drug (in any proportion) can be in the form of prodmg(s) of formula ϕ or pharmaceutically acceptable salts thereof and the other drug can be in its native form. For clarity, let us assume that Ibuprofen and Paracetamol are present as active principles in a pharmaceutical composition. Then, either or both of these drugs can be in their prodrug form (i.e., NO-Paracetamol and Ibuprofen/ Paracetamol and NO-Ibuprofen/ NO-Paracetamol and NO-Ibuprofen, etc.) and they can be present in any proportion.

15 It should also be understood that a pharmaceutical composition consisting of two or more of the above listed/qualified drugs, one of the drugs can be in the form of NO-releasing (matrix derivative) prodrug and the other drug(s) by the combination can be in the form another type of prodrug.

20 It should also be understood that a pharmaceutical composition containing a combination of one of the above listed/qualified drug(a) and its own prodrug is also covered (i.e., a pharmaceutical composition consisting of NO-Paracetamol and Paracetamol in any proportion). In such pharmaceutical compositions, the free drug will be useful for faster onset of action and the prodrug will be useful for extension of the duration of action as it releases the drug in a controlled fashion over a longer period of time. Such combination drug therapy may also minimize the toxicity and other side effects due to excessive plasma concentration of free drug. It should also be understood that a pharmaceutical combination may contain a prodrug of one of the above listed/qualified drugs and another type of prodrug of the same drug (e.g., NO prodrug of paracetamol and mutual prodrug of paracetamol with another drug) and these can be present in any therapeutic proportion depending on the medical need.

30

EXPERIMENTAL

ABBREVIATIONS USED;

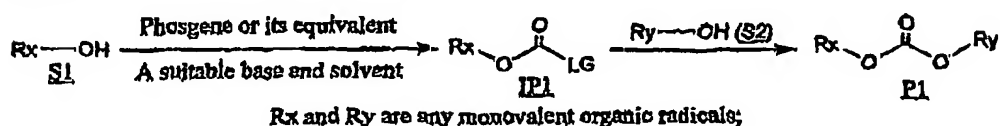
- BOP: Benzotriazol-1-yl-oxy-trimethylammonium hexafluorophosphate
 DMF: N,N-Dimethylformamide
- 5 DSC: N,N'-Pisucci trimethyl carbonate
 CDI: N,N'-Carbonyldiimidazole
 DTE; Dithioerythritol
 DTT: Dithiothreitol
 DCC: N,N'-Dicyclohexylcarbodiimide
- 10 EDAC, HCl: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
 HBTU-, 0«(Benzotriazol-1-yl-oxy-trimethylammonium hexafluorophosphate
 TBTU: 0«(Benzotriazol-1-yl-oxy-trimethylammonium hexafluorophosphate
 EtOH: Ethanol
 Et₂O; Diethyl ether
- 15 THF: Tetrahydrofuran
 DMSO: Dimethyl sulfoxide
 TEA: Triethylamine
 DIPEA: N,N-Diisopropylethylamine
 DCM: Dichloromethane
- 20 EtOAc: Ethyl acetate
 DME; Dimethoxyethane
 MeOH; Methanol
 PE; Petroleum ether
 RT; Room temperature
- 25 TFA: Trifluoroacetic acid
 HOBT: N-Hydroxybenzotriazole
 SYNTHETIC METHODS:

The prodrugs described herein can be prepared by any number of methods known to those skilled in the art. The synthetic approaches and the reagents are chosen depending upon the functional groups such as carboxyl, hydroxyl, amino or carbonyl groups present in the drug molecules to be used. The following illustrative

methods, as shown in Schemes 1 through 9, can be utilized to make carbonate, urethane, amide, ester, N-acyl carbamate, N-acyl amide, N-acyl sulfamate, and N-acyl sulfonamide, N-acyl phosphoramidate, N-oxycarbonylsulfonamide, N-oxycarbonylcarbamate linkages, etc. between drug(s) and linkers).

5 Methods of making carbonate linkages;

As depicted in the scheme 1, the carbonate linkage between the drug and the linker can be made by reacting the hydroxyl-containing drug (alternatively, hydroxyl group of the linker) with phosgene or its equivalents such as diphosgene, triphosgene, N,N'-Carbonyldiimidazole (CDI), N,N'-disuccinimidyl carbonate (DSC), 4-nitrophenyl chloroformate and the like, to give a reactive alkoxy carbonyl derivative, where LG is suitable leaving group such as a halide, imidazole, O-succinimide, 4-nitrophenoxide and the like, which can be reacted with hydroxyl group of the linker (alternatively, hydroxyl group of drug if the linker is converted to active alkoxy carbonyl derivative) in the presence of a suitable base and solvent

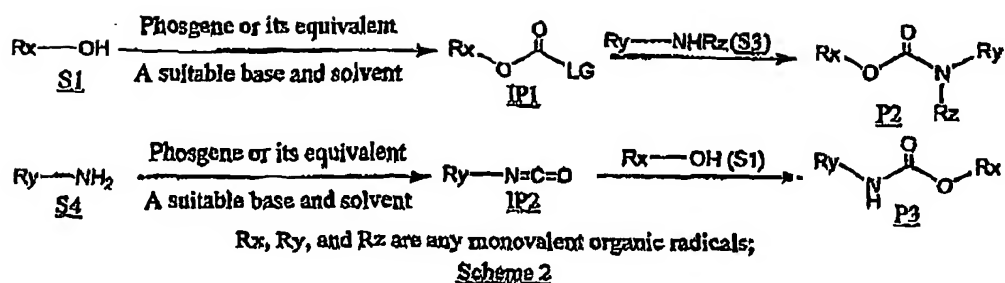


Scheme 1

Bases such as triethylamine, diisopropylethylamine, 4-(dimethylamino)pyridine (DMA?), and the like, can be used. Suitable solvents include CH₂Cl₂, CHCl₃, DMF, THF, ACN, ethyl acetate, ethyl ether and the like.

Methods of making urethane linkages;

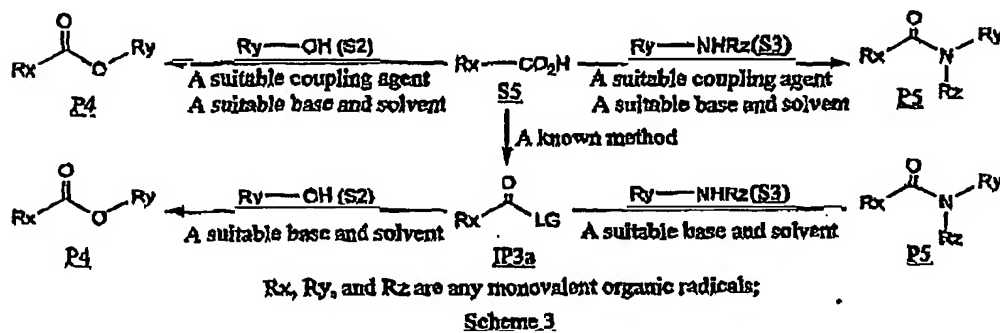
As shown in scheme 2, the urethane linkage between the drug and the linker can be made by reacting the hydroxyl-containing linker with phosgene or its equivalents (defined above) to give a reactive alkoxy carbonyl derivative, which can be reacted with amino-containing drug in the presence of a suitable base and solvent. Alternatively, a urethane linkage can be made by adding an alcohol to an isocyanate.



Suitable bases and solvents are same as defined above.

Method(s) of making amide or ester linkage(s);

As shown in the Scheme 3, an amide or ester linkage between the drug and the linker can be made by reacting a carboxyl-containing drug with an amino- or hydroxyl-containing *linker* in the presence of a suitable coupling agent, base and solvent. Alternatively, the carboxyl-containing compound can be first converted to reactive carbonyl derivative such as an acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazole and the like, which can be treated with amino-containing or hydroxyl-containing linker in the presence of a suitable base and solvent to afford the corresponding amide or ester linkage(s), respectively (see, Bodanszky, M. and Bodanszky, A., *The Practice of Peptide Synthesis*, Springer-Verlag, New York, 1984)

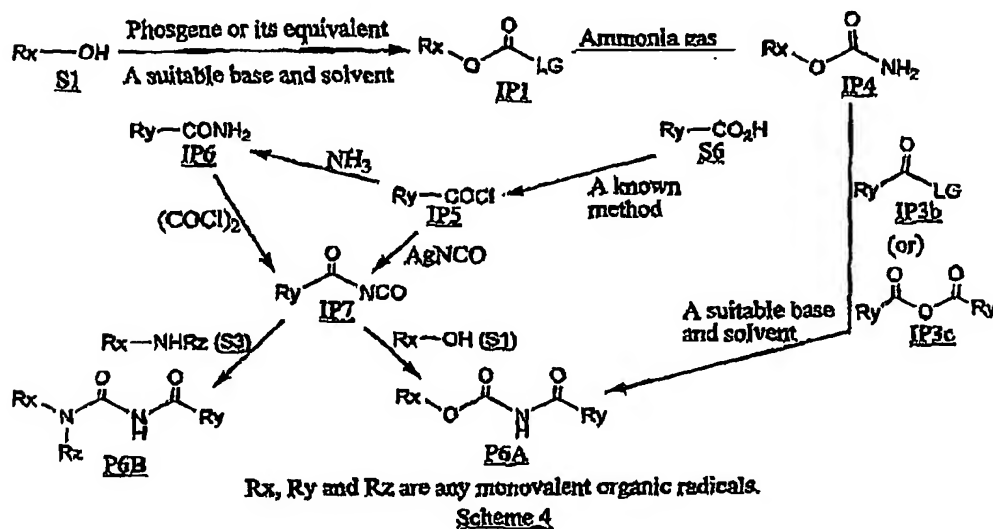


Suitable coupling agents include DCC, EDCLHCl, BOP, HBTXJ, TBTU, DCC/HOBT, EDC/HOBT, and the like. Suitable bases and solvents are same as defined above.

Method of making N-acyl carbamate and N-acyl urea linkage:

The linkage such as N-acyl carbamate linkage between the linker and drug can be made as shown in Scheme 4. The treatment of an alcohol with phosgene or its

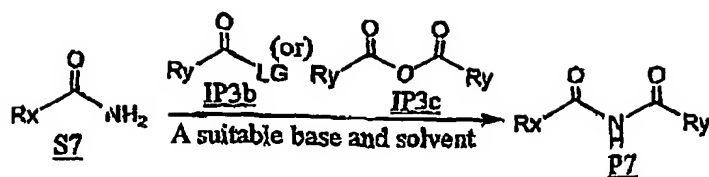
- equivalent can yield the corresponding carbonochloride, which upon treatment with ammonia gas can give the corresponding carbamate intermediate. The carbamate nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazole, and the like, in the presence of a suitable base to yield the corresponding N-acyl carbamate. Alternatively, N-acyl carbamate can be made by the reaction of an alcohol with N-acyl isocyanate, which can be prepared either by the reaction of the corresponding amide with phosgene chloride (See, Speziale, A. J., et al., J. Org. Chem. 1962, 27, 3742; Speziale, A. J., et al., J. Org. Chem. 1963, 28, 1805-1810) or by the reaction of the corresponding acid chloride with silver cyanate. (See, Hill, A. J. et al., J. Am. Chem. Soc., 1940, 62, 1595; Kim, D.K. J. Heterocyclic Chem. 1995, 32, 1625).



Suitable bases and solvents are same as defined above.

Methods of making N-acyl amide linkage:

- The TSt-acyl amide linkage between the linker and drug can be made as shown in Scheme 5. Thus, the amide nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazole, and the like, in the presence of a suitable base to yield the corresponding N-acyl amide.



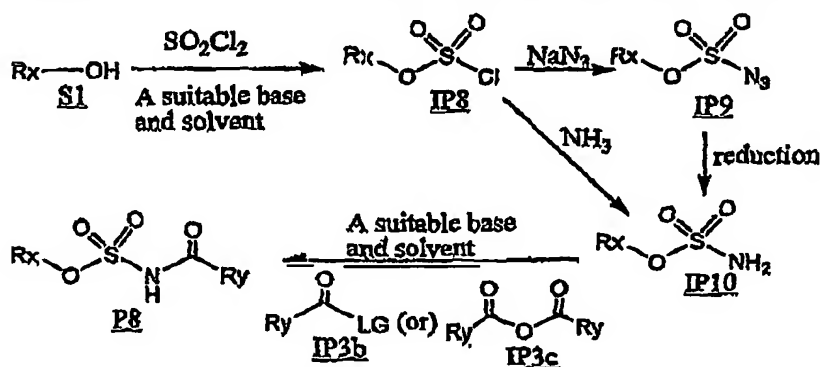
Rx and Ry are any monovalent organic radicals.

Scheme 5

Suitable bases and solvents are same as defined above.

Methods of making N-acyl sulfamate linkages:

5 The linkage such as N-acyl sulfamate between the linker and drug can be made as shown in Scheme 6. Thus, treatment of an alcohol with sulfuryl chloride in the presence of suitable base gives the intermediate sulfonyl chloride, which can be converted to the corresponding sulfonate. Acylation of sulfonate nitrogen with a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazoline, and the like, can yield the corresponding N-acyl sulfamate.



Rx and Ry are any monovalent organic radicals.

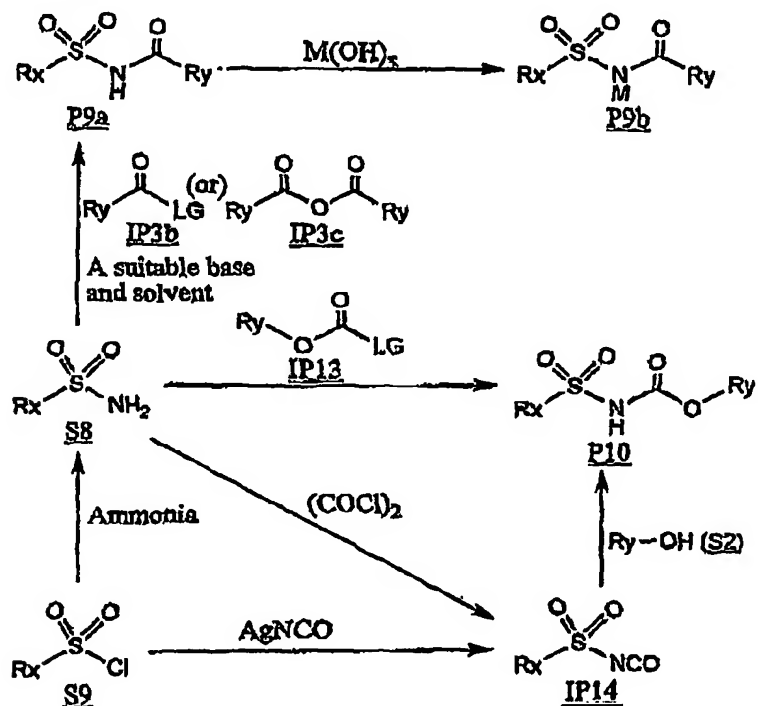
Scheme 6

Suitable bases and solvents are same as defined above.

Methods of making N-acyl/oxy carbonyl sulfonamide linkages:

15 The N-acyl/oxy carbonyl sulfonamide linkage between the linker and drug can be made as shown in Scheme 7. Thus, a sulfonamide nitrogen can be acylated by a suitable carboxylic acid derivatives such as anhydride or acid halide, a succinimide ester, a pentafluorophenyl ester, an imidazoline, and the like, to yield the corresponding N-acylsulfonamide, which can be meta-located using an inorganic base. Similarly, the

- 5 sulfonamide nitrogen can be acylated by a suitable formyl chloride derivative such as alkyloxycarbonyl chloride, imidazolide and the like, to yield the corresponding N-alkyloxycarbonyl sulfonamide as shown in the scheme. Alternatively, the same linkage can be made by the reaction of an alcohol with sulfonyl isocyanate which can be prepared by known methods such by treatment of sulfonamide with oxalyl chloride (see, Hans McCalla et al., US2666787 or Smith, I et al., J. Org. Chem. 1965, 30, 12604262) or by treatment of sulfonyl chloride with silver cyanate (See, Smith, J. et al, J. Org. Chem, 1965, 30, 1260-1262).



Rx, and Ry are any monovalent organic radicals; M is a metal ion; x is 1-4

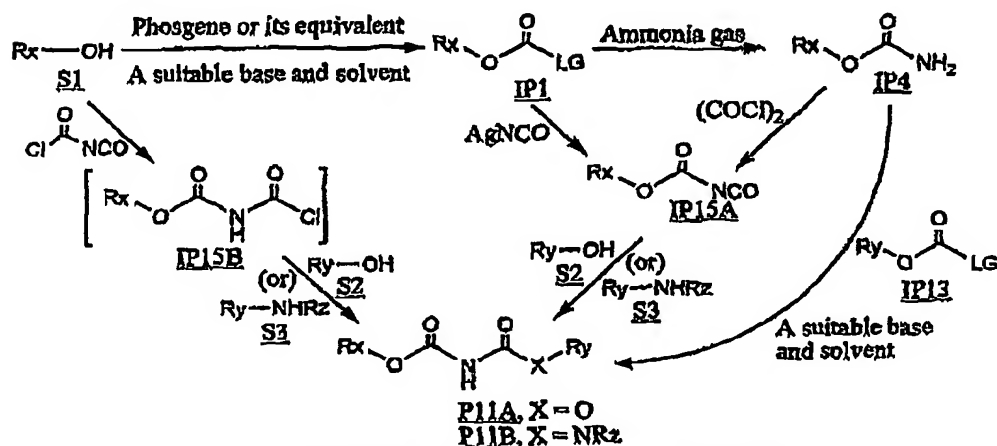
Scheme 7

- 10 Suitable bases and solvents are same as defined above.

Methods of making N-alkyloxycarbonyl sulfonamide and N-alkyloxycarbonyl sulfonamide linkages:

The N-alkyloxycarbonyl sulfonamide (or N-alkyloxycarbonyl sulfonamide) linkage between the linker and drug can be made as shown in Scheme S. Thus, sulfonamide nitrogen can be acylated by suitable formyl chloride derivatives such as alkyloxycarbonyl chloride,

imidazolidine and the like, to yield the corresponding N-alkyloxycarbonyl carbamate as shown in the scheme. Alternatively, the N-oxycarbonylurea (or N-oxycarbonylurea) linkage between the linker and drug can be made by the reaction of an alcohol (or an amine) with carbamoyl isocyanate (IP15A), which can be prepared by known methods such as by treatment of carbamate with oxalyl chloride (See, Greife JL, et al., Synthesis, 1988, 922-994) or by treatment of a formyl chloride with silver cyanate (See, Kim, N.K. et al., J. Heterocyclic Chem. 1995, 32, 1625). Alternatively, N-oxycarbonyl carbamate (or N-oxycarbonylurea) can be prepared in two steps. Step 1: reaction of an alcohol or phenol with chlorocarbonyl isocyanate to give N-oxycarbonyl carbamoyl chloride intermediate (IP15B). Step 2: reaction of the intermediate IP15B with the same or another alcohol or phenol or an amine. (For a review on chemistry of chlorocarbonyl isocyanate, see, Gorbatevko, V. I. Tetrahedron, 1993, 49, 3227),



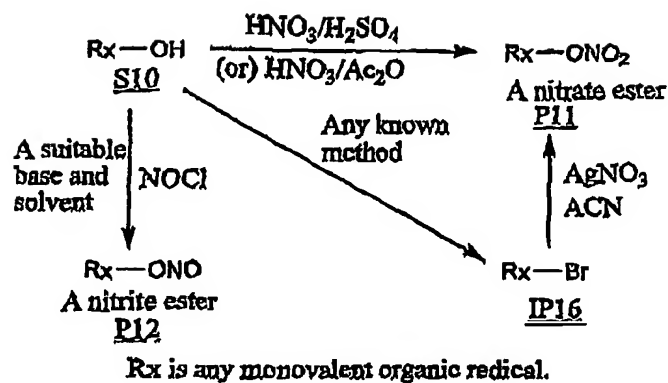
Rx, Ry and Rz are any monovalent organic radicals.

Scheme 8

Suitable bases and solvents are same as defined above.

15 Methods of making Nitrate, nitrooxy, nitroxy-oxV, ester&i

The nitrate or nitrite esters can be made as shown in Scheme 9. Thus, a nitrate or nitrite ester can be made by treating an alcohol with $\text{HNO}_3/\text{H}_2\text{SO}_4$ (or HNO_3/AcOH) or nitrosyl chloride, respectively. Alternatively, a nitrate ester can be made by treating a halide (bromide or iodide is preferred) with silver nitrate in a polar aprotic solvent such as acetonitrile.



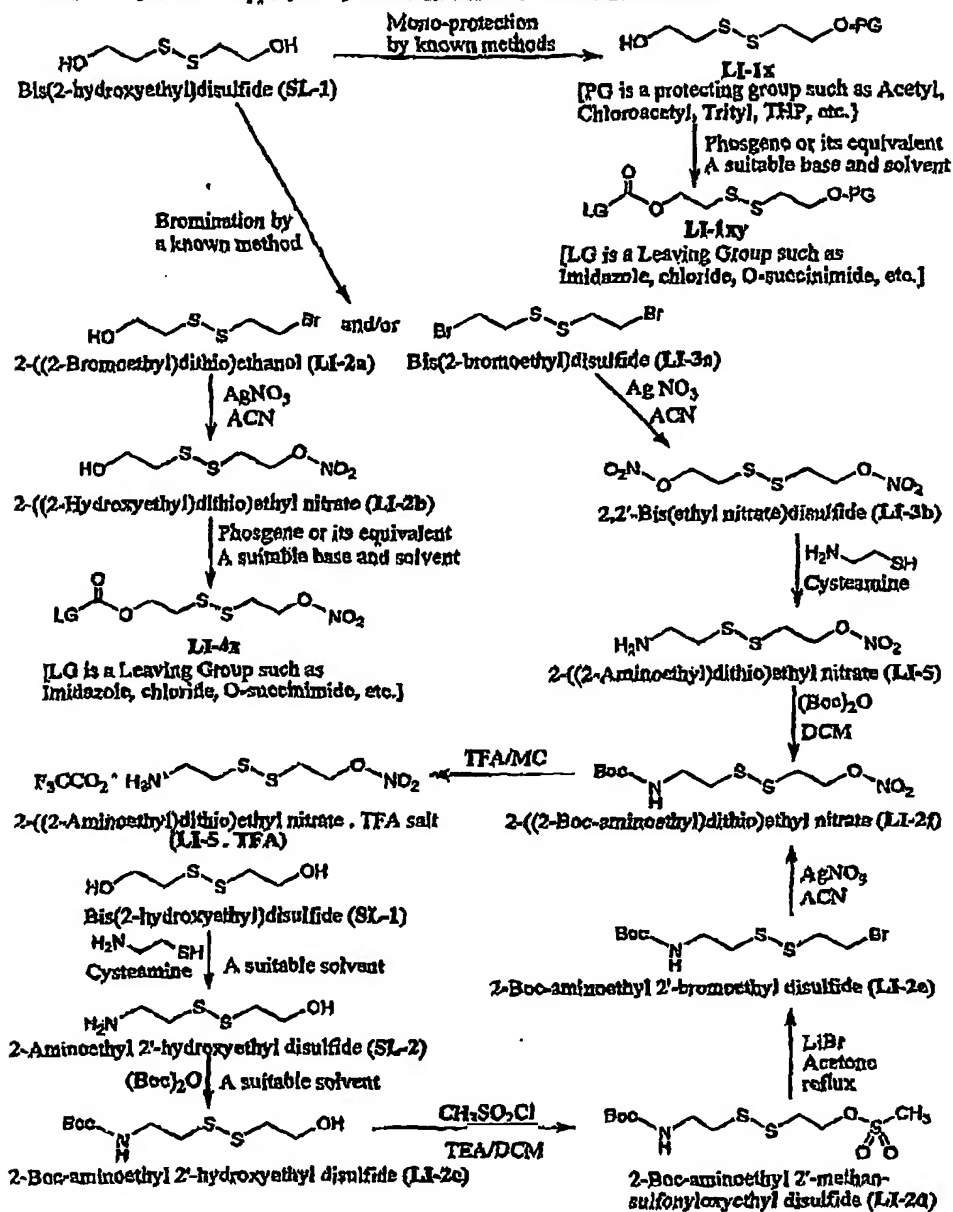
Scheme 9

Compounds (Prodrugs) of the formula Q containing bio-cleavable linker and linkages can be synthesized by various methods obvious to those skilled in the art. As a matter of illustration, any of the approaches shown in the following schemes can be used to make such prodrugs of the foregoing (Q) described herein.

- Monoprotection of diol or aminoalcohol or diamine compounds [i.e., linker(s)] with suitable protecting groups and their selective removal at appropriate stage of the synthesis are carried out as described in, Theodore W. Greene and Peter O.M. Wuts, "Protective Groups in Organic Synthesis", 3rd edition, John Wiley and Sons, Inc. New York (1999), the disclosures of which are incorporated herein by reference. Suitable protecting groups (PGs) include, but are not limited to, acetyl, Boc, Fmoc, benzoyl, pivaloyl, trityl, tetrahydropyranyl (THP), and silyl (TBDMS, XMS, etc.). Obviously, selection of a suitable protecting group is very crucial for the success of a chosen method for the synthesis of prodrugs described in the invention.

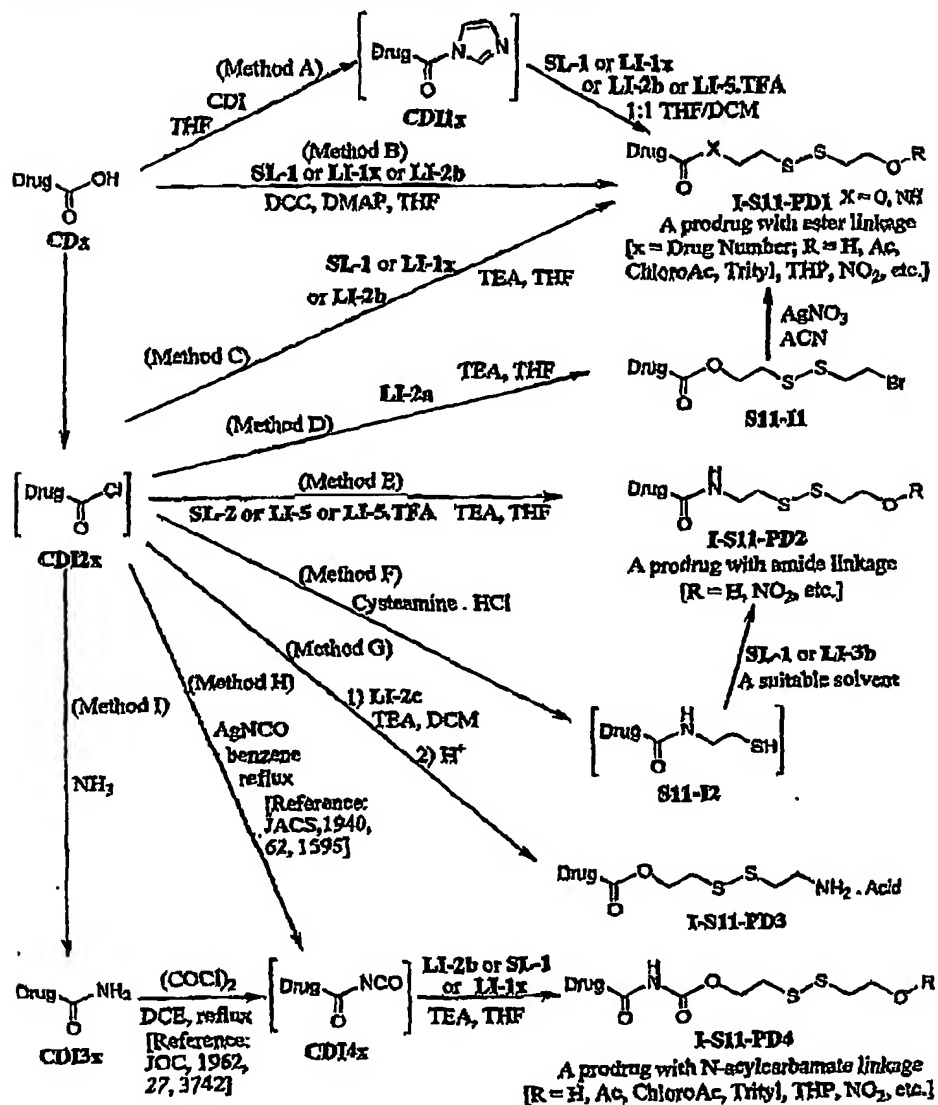
Synthesis of appropriately derivatized suitable linker is shown in Scheme 10.

Scheme 10: Synthesis of appropriately derivatized/modified linker intermediates

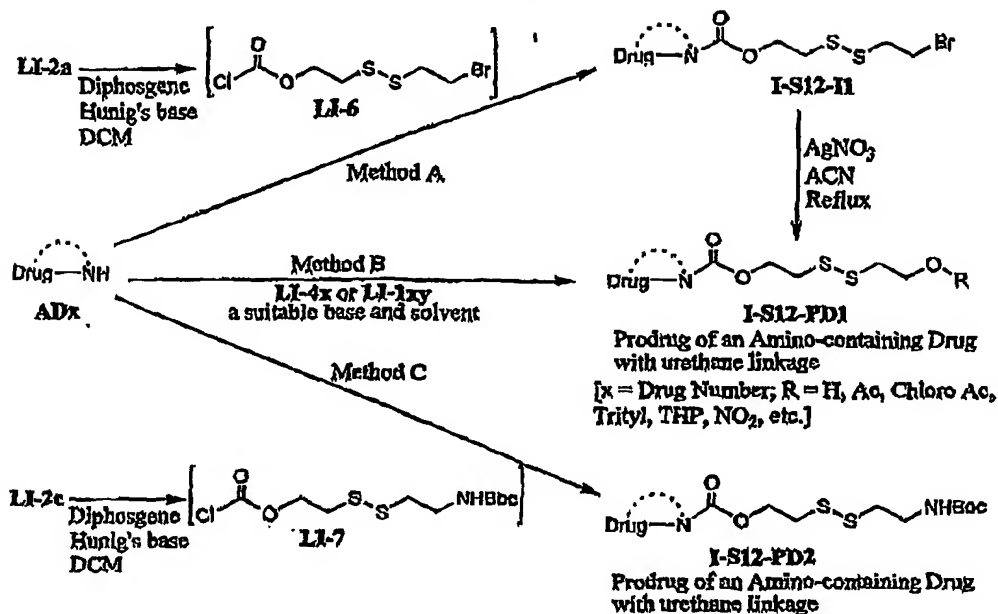


Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs) of carboxyl-, amino-, and hydroxyl-containing drugs are shown in Schemes 11 through 14.

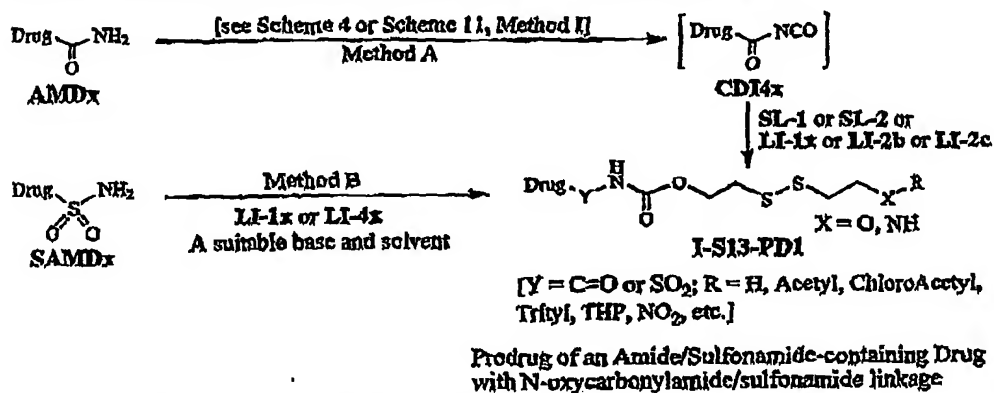
Scheme 11: Synthesis of Prodrugs of Carboxyl-containing Drugs



Scheme 12: Synthesis of Prodrugs of Amino-containing Drugs



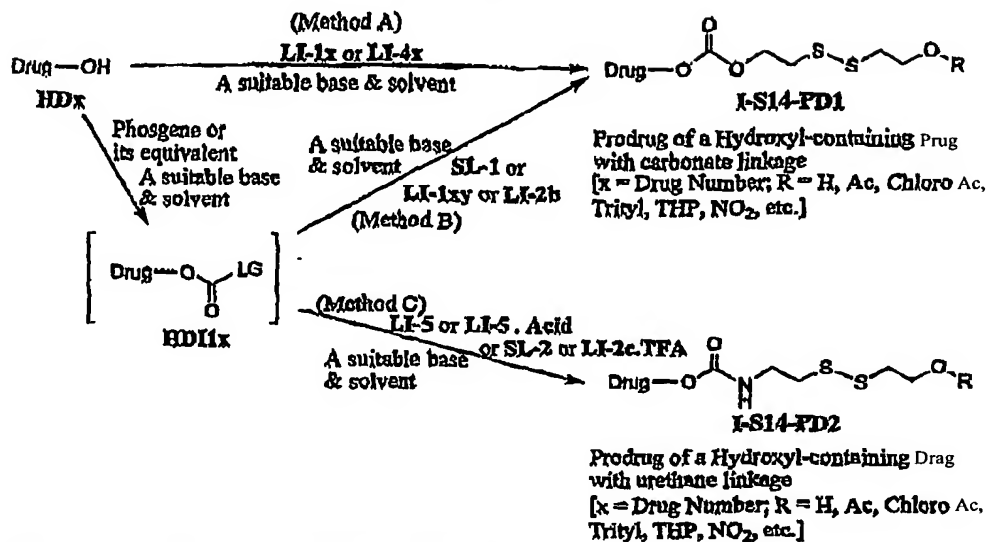
Scheme 13: Synthesis of Prodrugs of Amide/Sulfonamide-containing Drugs:



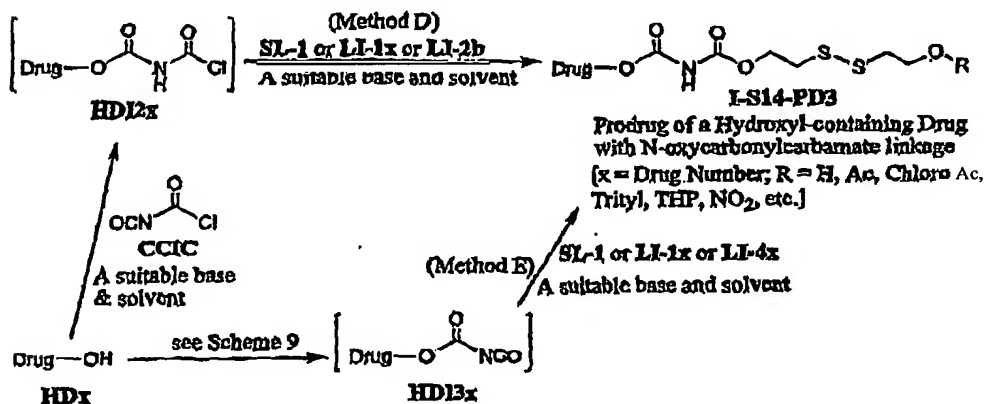
AMDx is a CONH₂-containing drugs such as vapromide, levosiracetam, carbamazepine, and the like.
 SAMDx is a SO₂NH₂-containing drugs such as valdecoxib, celecoxib, and the like.

Scheme 14: Synthesis of Prodrugs of Hydroxyl-containing Drugs

A) Prodrugs with carbonate and carbamate linkages:

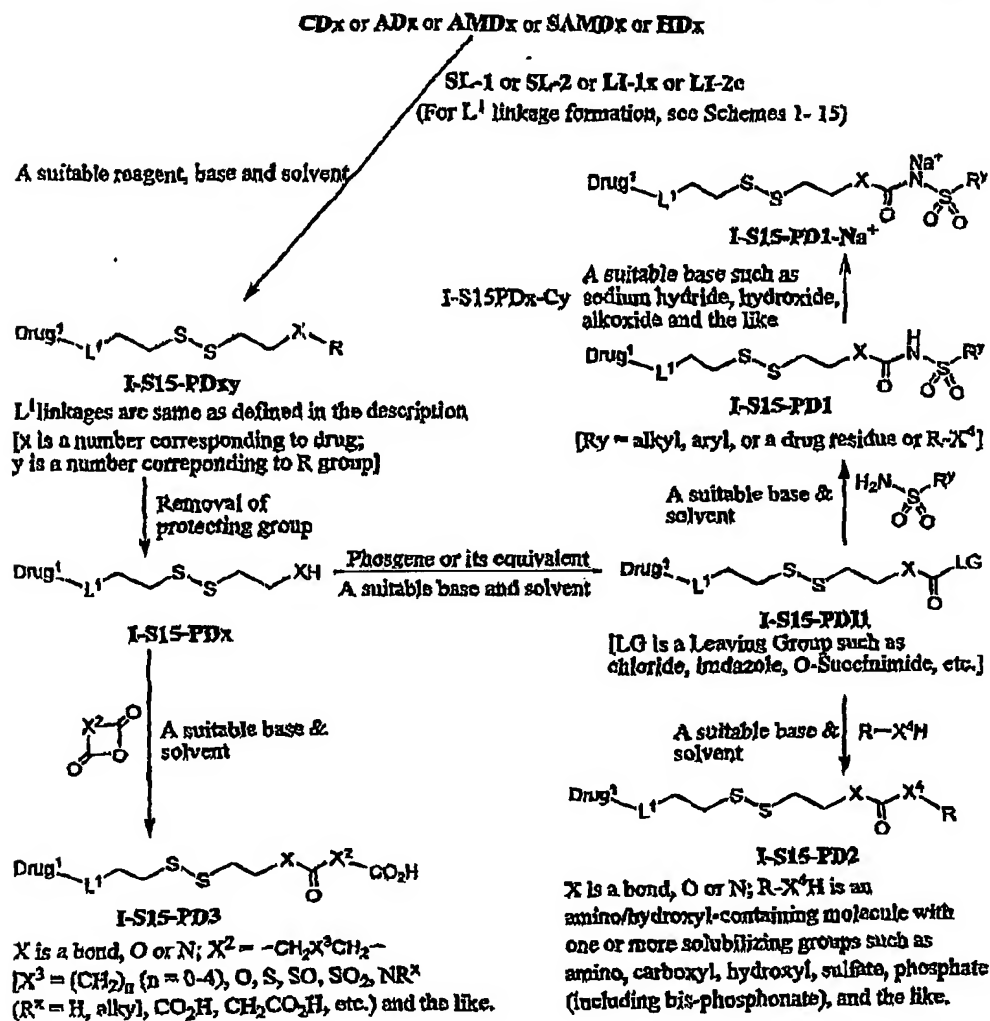


B) Prodrugs with N-oxycarbonylcarbamate linkage:

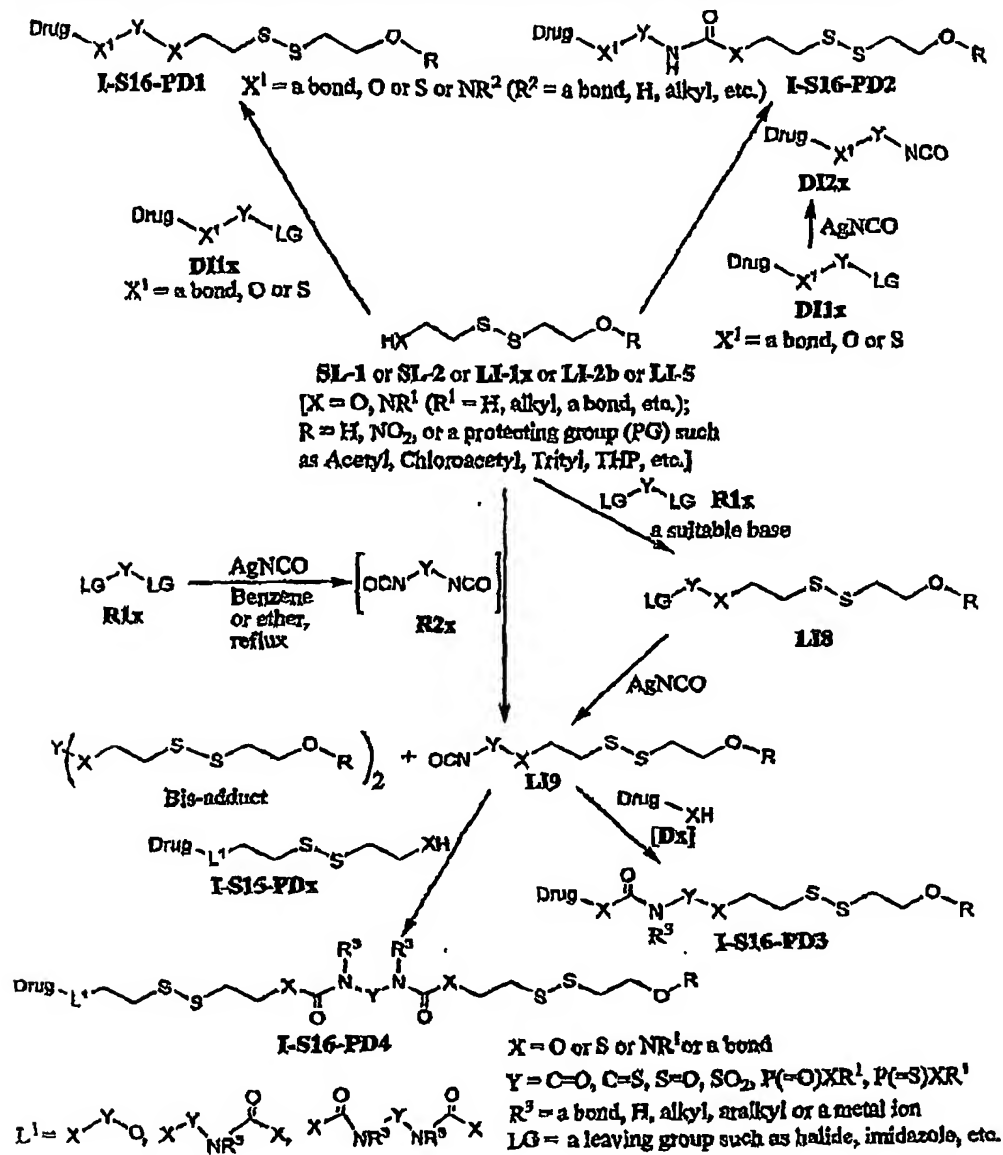


Some of the methods for the synthesis of prodrugs (including NO-releasing prodrugs and water-soluble prodrugs) are shown in Schemes 15 and 16.

Scheme 15: Synthesis of Water-soluble Prodrug(s) using a bio-cleavable linker(s) and spacer linker (s)

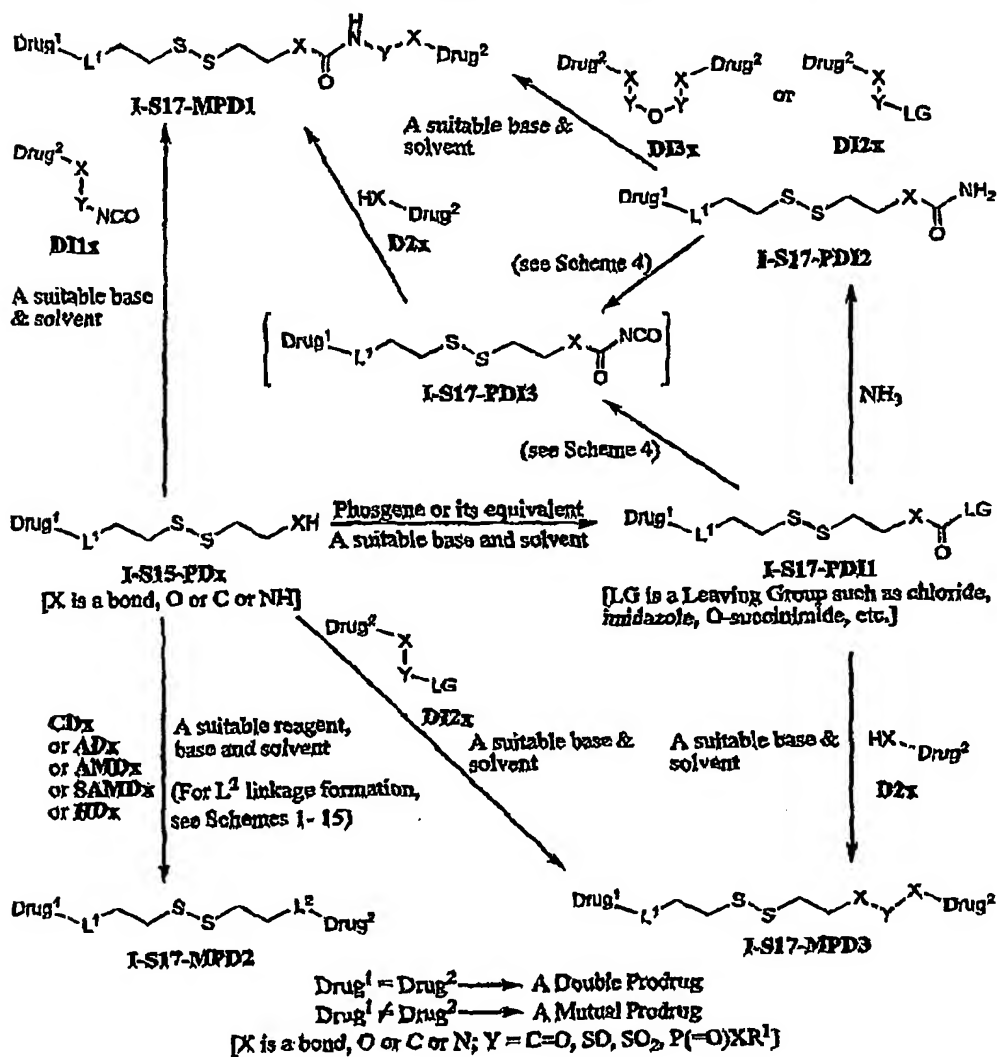


Scheme 16: Synthesis of Prodrugs containing a biocleavable linker and various types linkages

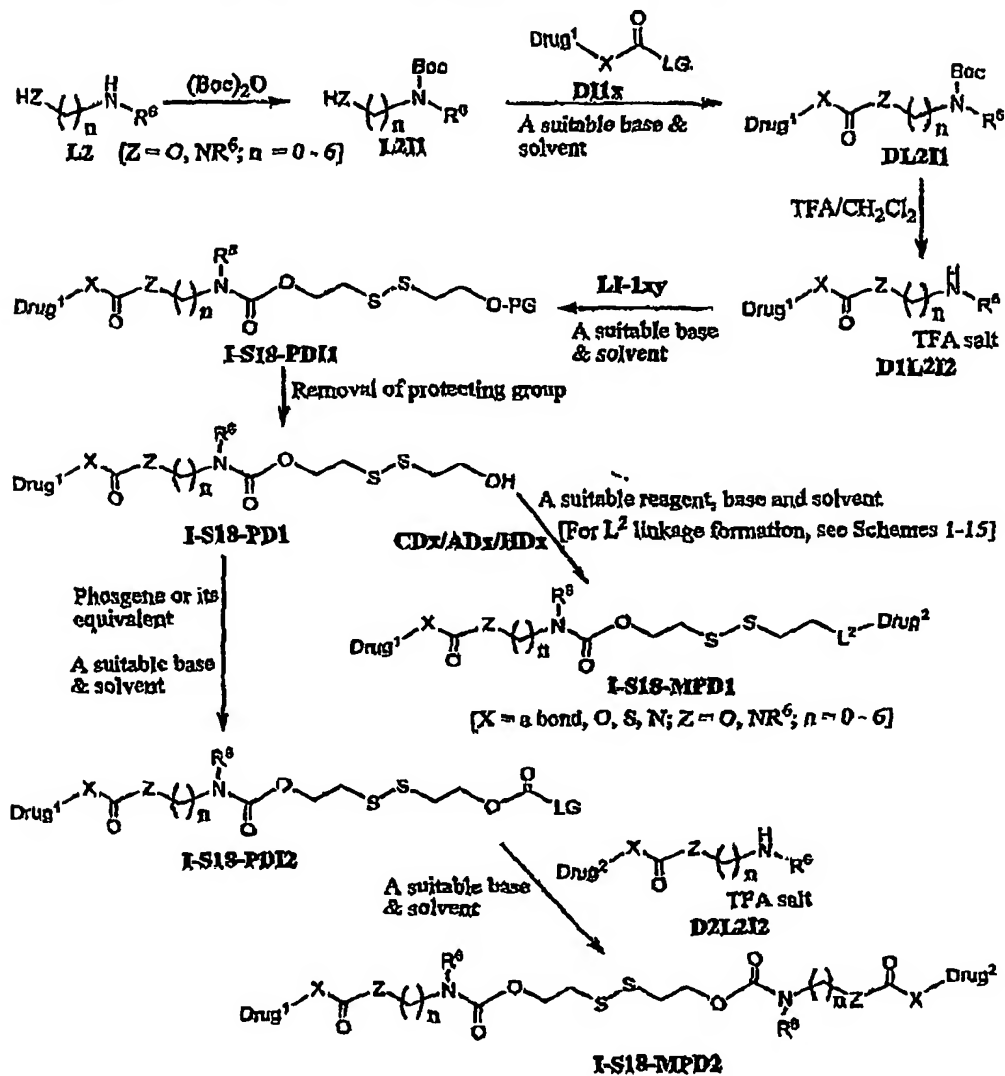


Double/Mutual prodrugs described in this invention can be synthesized by any of the approaches depicted in Schemes 17 through 19.

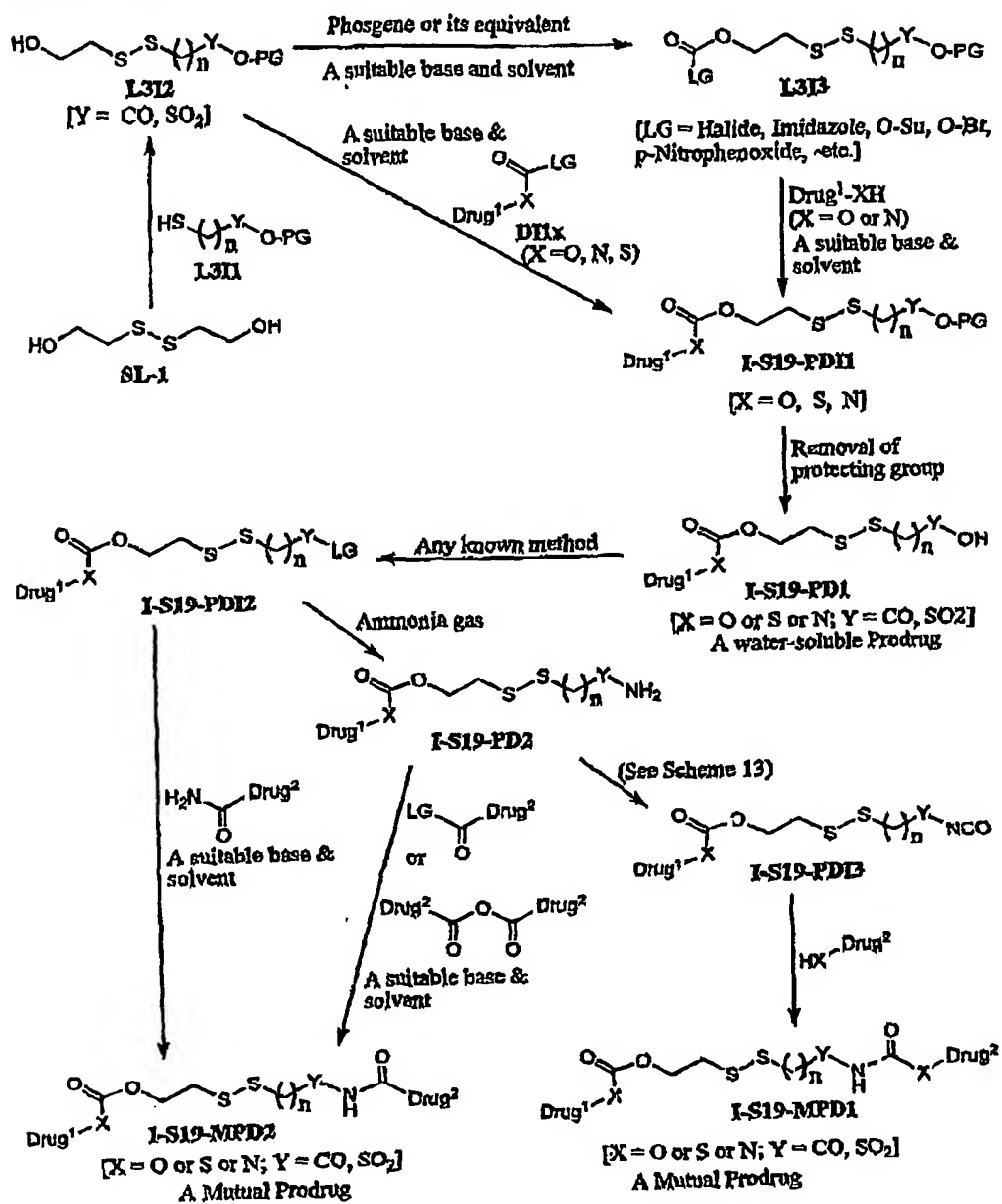
Scheme 17: Synthesis of Mutual Prodrug(s) using a bio-cleavable linker(s) and spacer linker(s)



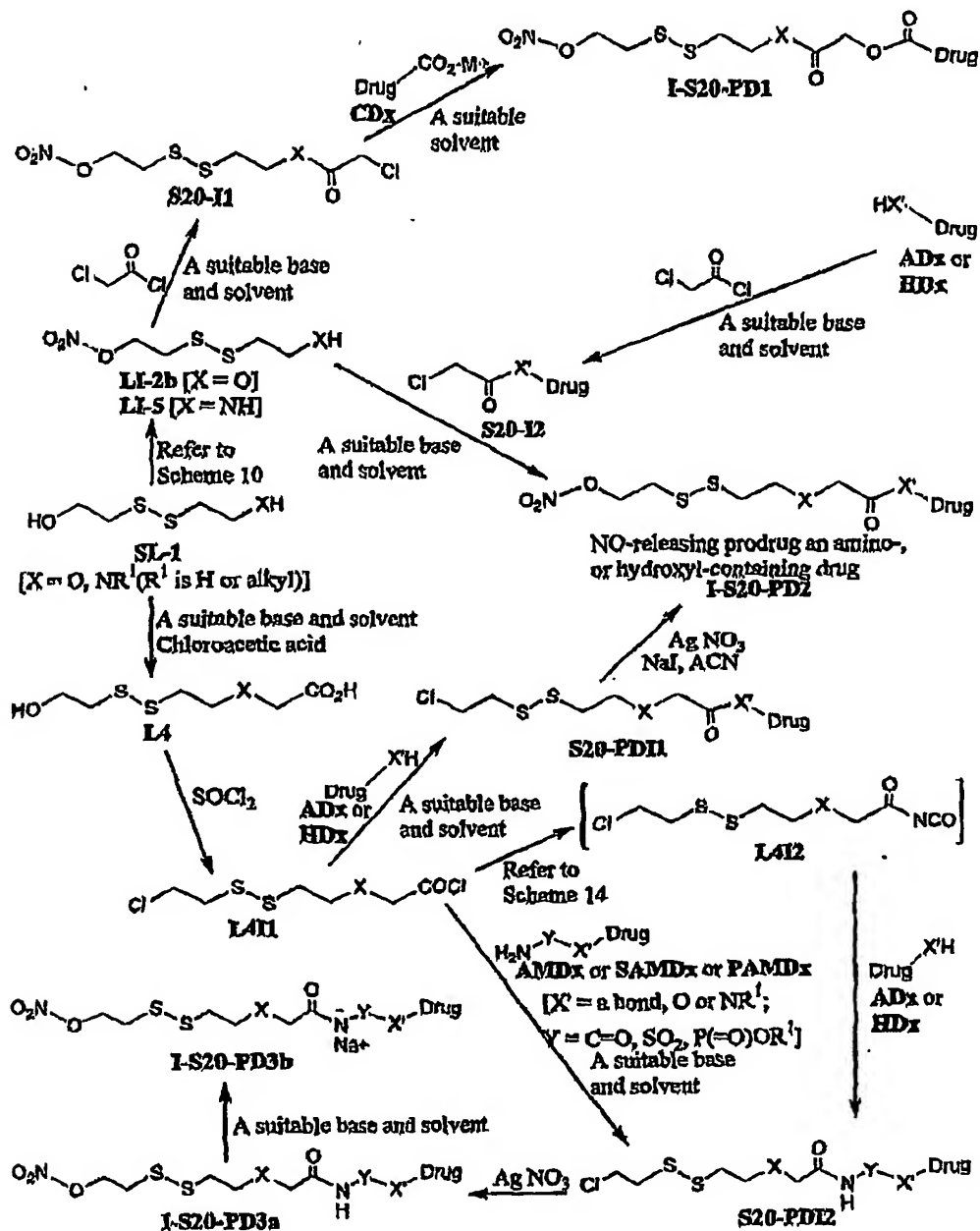
Scheme 13: Synthesis of Double/Mutual Prodrug(s) with additional linkers



Scheme 19: Synthesis of Mutual Prodrug(s) using modified bio-cleavable linker(s)

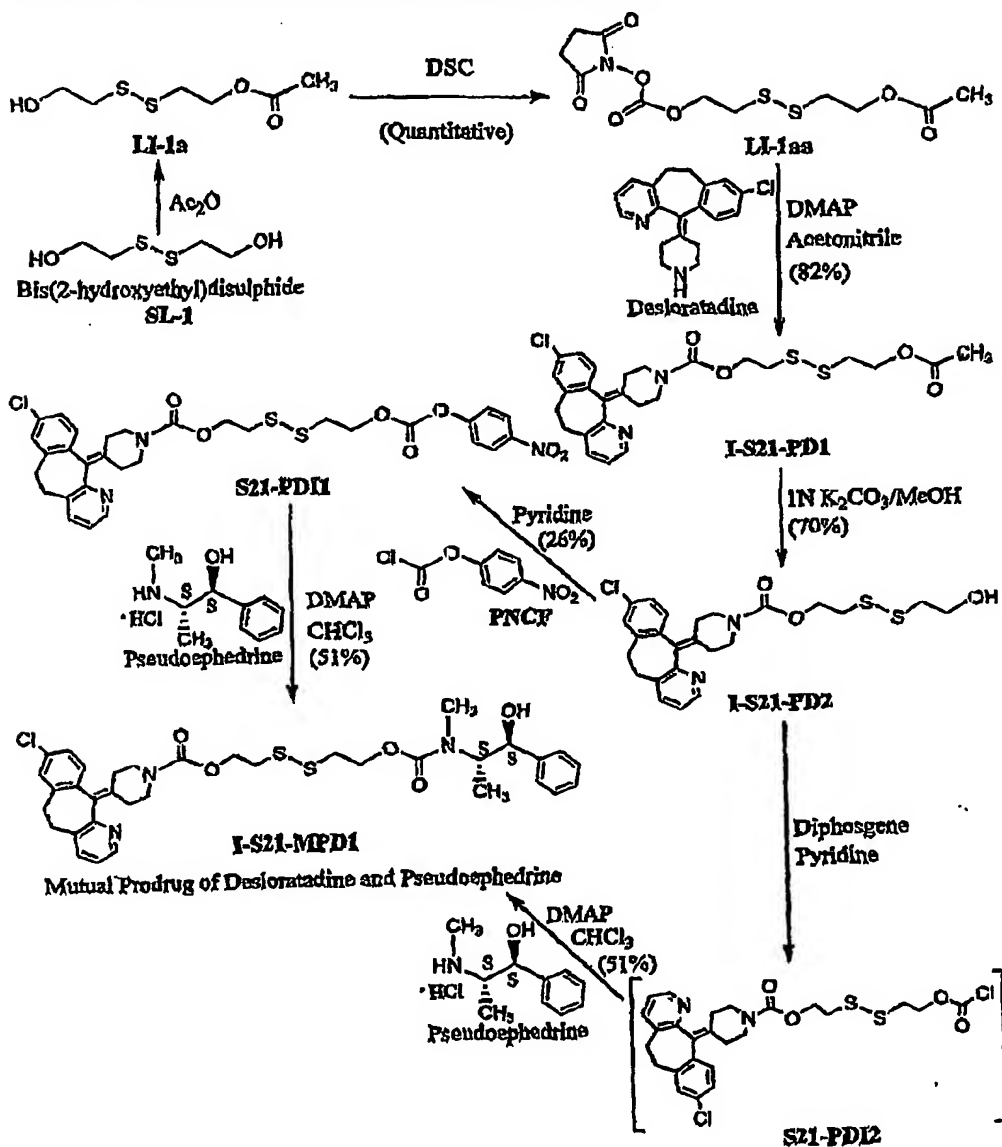


Scheme 20: Synthesis of Mutual Prodrug(s) using modified bio-cleavable linker(s)

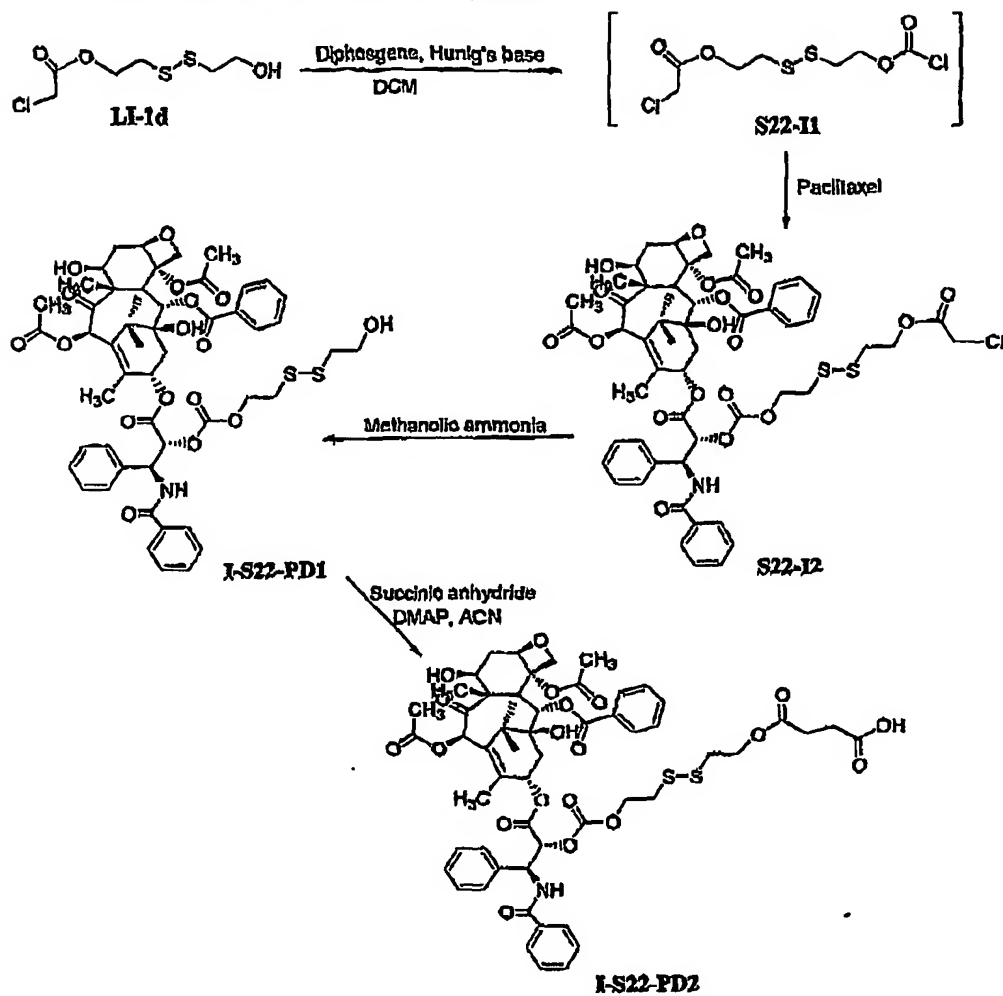


As a matter of illustration, mutual prodrug of desloratadine and pseudoephedrine
is synthesized as depicted in Scheme 21.

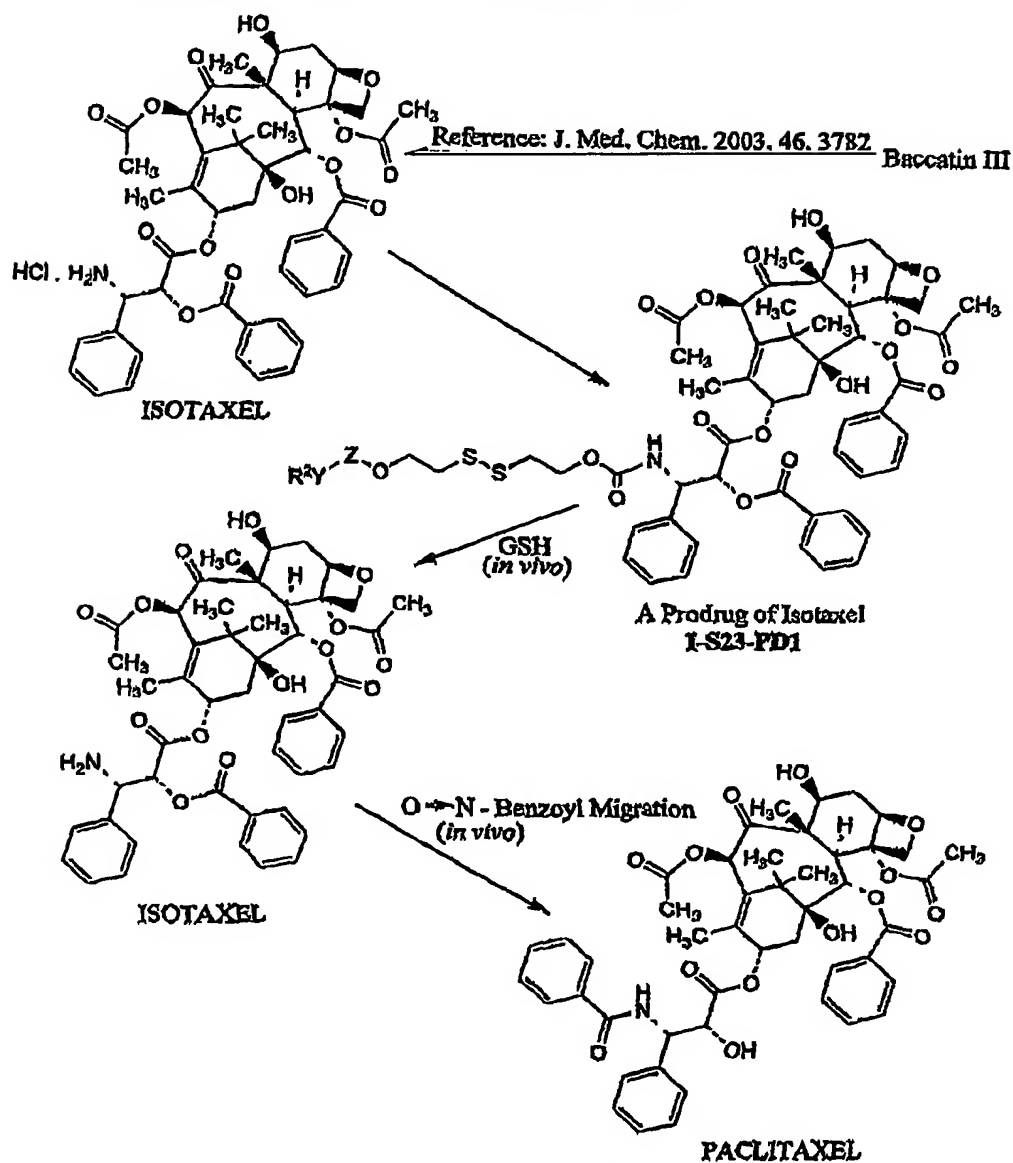
Scheme 21: A Mutual Prodrug of Desloratadine and Pseudoephedrine



Scheme 22: Synthesis of a water-soluble prodrug of paclitaxel



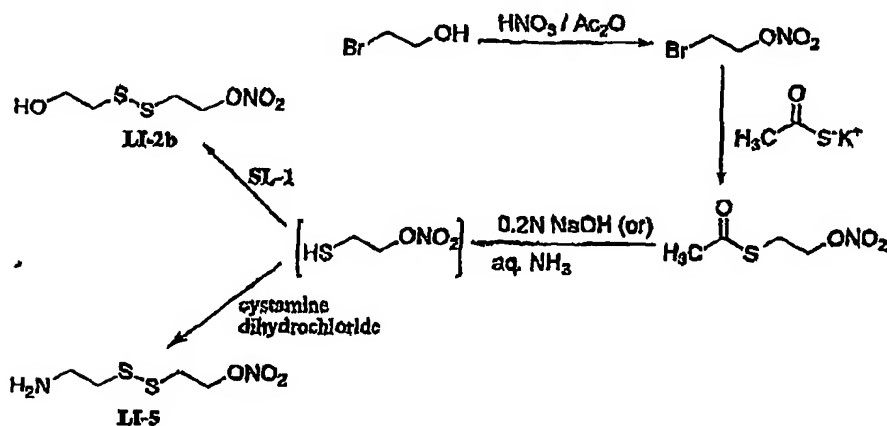
Scheme 23: Generation of Paclitaxel from a Prodrug of Isotaxel



$\text{Y} = \text{O}, \text{NR}^1$ ($\text{R}^1 = \text{H}, \text{Alkyl}, \text{Aryl}, \text{Cycloalkyl}, (\text{CH}_2)_n\text{C}(=\text{O})$ ($n=1-6$), $(\text{CH}_2)_n\text{CO}_2^-$)

$\text{Z} = \text{C}=\text{O}, \text{SO}_2, \text{P}(=\text{O})\text{YR}^3$ ($\text{R}^3 = \text{H}$ or a metal ion)

$\text{R}^2 = \text{H}, \text{a bond}, \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2, \text{HCl}, \text{an Amino acid}, \text{or any molecule containing solubilizing groups such as carboxylic acid, sulphonic acid, hydroxyl, amino groups, polyethyleneglycol (PEG), a metal ion such as } \text{Na}^+, \text{Ca}^{2+}, \text{etc.}$

Scheme 24: An alternative method for the synthesis of Linker Intermediates **LI-2b** and **LI-5**

Example 1

Synthesis of 2-[(2-hydroxyethyl)dithio]ethyl acetate (**LI-1a**):

Acetic anhydride (5.67 g, 56.87 mmol) and pyridine (40.4 ml, 499 μmol) were added to a solution of 2-[(2-hydroxyethyl)dithio]ethyl acetate (**SL-1**, 15.39 g, 99.78 μmol) in DCM (350 mL) at RT and the mixture was stirred at RT for 16 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 5.16 g (42%) of **LI-1a** as a pale yellow oil. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.00 (bs, 1H), 2.08 (s, 3H), 2.80-2.95 (m, 4H), 3.89 (t, 2H, $J = 6$ Hz), 4.35 (t, 2H, $J = 6$ Hz), MS: (m/z) 219 [M].

Example 2

Synthesis of 2-[(2-hydroxyethyl)dithio]ethyl acetate (**LI-1b**):

This compound was synthesized by a method described by K. R. Bemady *et al.* *J. Org. Chem.*, 1979, 44, 1438. Dihydropyran (5.41 g, 100 μmol) was added to a solution of **SL-1** (15.4 g, 100 μmol) in DCM (200 mL) at 0-5 $^\circ\text{C}$, followed by PT8A (-5%) and stirred at RT for 5 h. The mixture, after usual aqueous work-up and chromatographic purification, afforded 14.5 g (50%) of **LI-1b**. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.5-1.9 (m, 6H), 2.88 (t, 2H, $J = 6$ Hz), 2.94 (t, 2H, $J = 6$ Hz), 3.45-3.57 (m, 1H), 3.57-3.78 (m, 1H), 3.85-4.05 (m, 2H), 3.90 (t, 2H, $J = 6$ Hz), 4.65 (s, 1H).

Example 3

Synthesis of 2-[(2-(2-hydroxyethyl)dithio)ethyl]acetate (**LI-1c**):

- This compound was synthesized by a method described by O. Hernandez *et al.*, *Tetrahedron Letters*, **1981**, 22, 149M494. Thus, 8.58 g (21.4 mmol) of 4-dimethylamino-N-phenyl- β -thiopyridinium chloride (A.V. Bhatfa *et al.*, *Organic Synthesis*, **1997**, ZJ, 184-185) was added to a solution of **SL-I** (3.0 g, 19.45 mmol) in DCM (90 mL) and stirred at RT for 24 h. The mixture, after usual aqueous work-up and chromatographic purification, afforded 2.86 g (37%) of **LI-Ic**. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.70 (t, 2H, $J = 6.0$ Hz), 2.88 (t, 2H, $J = 6.0$ Hz), 3.39 (t, 2H, $J = 6.0$ Hz), 3.80 (q, 2H, $J = 6.0$ Hz), 7.24-7.33 (m, 1H), 7.44-7.46 (m, 5H). MS (m/z): 396 $[\text{M}]^+$.

Example 4

- 10** Synthesis of chloroacetic acid 2-(2-hydroxyethylthio)ethyl ester (**LI-Id**): To a solution of **SL-I** (23 g, 150 mmol) in DCM (250 mL) at 0 °C were added TEA (10.12 g, 100 mmol) and chloroacetyl chloride (11.3 g, 100 mmol) and stirred overnight at RT. The reaction mixture was concentrated and purified by column chromatography to afford 8.3 g (37%) of **LI-W**. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.88 (t, 2H, $J = 5.7$ Hz), 2.95 (t, 2H, $J = 6.6$ Hz), 3.89 (t, 2H, $J = 5.7$ Hz), 4.05 (s, 2H), 4.47 (t, 2H, $J = 6.6$ Hz),

Example 5

Synthesis of 2-((2-hydroxyethyl)dithio)ethyl nitrate (**LI-2b**) and 2,2'-bis(ethyl nitratethio)disulfide (**LI-3b**):

These intermediates were synthesized in two steps as shown in Scheme 10.

- 20** Step 1: Synthesis of 2-((2-bromoethyl)dithio)ethyl nitrate (**LI-2a**) and bis(2-bromoethylthio)disulfide (**LI-3a**): These compounds can be synthesized *via* bromination of **SL-I** by a known bromination method. (For a suitable bromination method, see Eruniss, B.S. *et al.*, Vogel's Text Book of Practical Organic Chemistry, 5th edition, Pearson Education, Singapore, 1989; pp 559-579). The following methods were explored:
- 25** Method 1: To a solution of **SL-I** (15 g, 97.4 mmol) in DMP (50 mL) was added PPh_3 (25.5 g, 97.4 mmol) and cooled to 0 °C. Bromine (3.33 mL, 64.9 mmol) was added dropwise and stirred at RT for 18 h. ILC of the mixture showed a mono-bromide derivative **LI-2a** as the major product with only trace amounts of dibromide **LI-3a**. The mixture was diluted with water and extracted with EtOAc . After usual aqueous work-up and chromatographic purification 3.65 g (26%) of **U-2a** were obtained. $^1\text{H-NMR}$ (300 MHz,

CDCl_3): 6 1.82 (s, 1H), 2.88 (t, 2H, $J = 5.8$ Hz), 3.08 (t, 2H, $J = 7.90$ Hz), 3.63 (t, 2H, $J = 7.90$ Hz), 3.90 (t, 2H, $J = 5.8$ Hz).

Method 2: To a solution of SiI (40 g, 0.26 mol) in DCM (400 mL) at 0°C was added a solution of OPBr_3 (24.62 g, 0.26 mol) in DCM (50 mL) and the mixture was stirred at RT for 15 min. TLC indicated formation of LI-3a as the major product with trace amounts of LI-2f. The reaction was quenched by the addition of water and extracted with DCM. After usual aqueous work-up and chromatographic purification, 33 g (45.3%) of LI-3a were obtained. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 6 3.1-3.15 (m, 4H), 3.60-3.66 (m, 4H). MS (Cl^-) m/z : 277.69 ($\text{M}+\text{H}^+$), 279.66. An alternative synthesis of LI-3s has been reported.

(Sharma, M. et al., *Bioorg. Med. Chem. Lett.*, 2004, 14, 5347-5350).

Method 3: To a cold suspension of SM (20 g, 129 mmol) in PCN (400 mL) was added CBr_4 (42 g, 129 mmol) and stirred for 10 min. PPh_3 (34 g, 129 mmol) was then added and stirred at RT for 14 h. The reaction mixture was concentrated and the residue purified by column chromatography to give 13.5 g (52.3%) of LI-2a and 13.0 g (36%) of LI-3a.

These compounds were identical (by TLC, NMR and MS) to those obtained in Methods 1 and 2 described above.

Synthesis of 2-((2-hydroxyethyl)thio)ethyl nitrate (LI-2b): To a solution of LI-2a (2g, 9.21 mmol) in acetonitrile (15 mL) was added AgNO_3 (1.55g, 11.05 mmol) portion-wise and the mixture was stirred at RT in the dark for 45 min. The reaction mixture was filtered through celite and the filtrate was concentrated. The residue after usual aqueous work-up and chromatographic purification gave 1.46 g (74%) crude LI-2b - which was used for the next reaction without further purification. An analytical sample was obtained by chromatographic purification. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.89 (t, 2H, $J = 6.0$ Hz), 2.98 (t, 2H, $J = 7.5$ Hz), 3.90 (t, 2H, $J = 6.0$ Hz), 4.74 (t, 2H, $J = 7.5$ Hz); MS (EI^+) (m/z): 161 (M^+).

Synthesis of 2,2'-bis(ethyl nitrate)diethyl sulfide (LI-3b): AgNO_3 (8.01 & 47.12 mmol) was added portion-wise to a solution of LI-3a (6.0 g, 21.42 mmol) in acetonitrile (40 mL) at RT in the dark and stirred for 30 min. The mixture was filtered through celite and the filtrate was concentrated in vacuo at 35°C to afford 4.6 g (35%) of LI-3b, which was used without further purification. An analytical sample was obtained by chromatographic

purification (3-15% BtOAc in petroleum ether). $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.10 (t, 4H, J = 6.3 Hz), 4.41 (t, 4H, J = 6.3 Hz). MS (EI) $^+$ m/z: 244 (M) $^+$.

Example 6

5 Synthesis of tert-butyl 2-((2-((tert-butoxy)amino)ethyl)carbamate (U-2c): To a solution of cysteamine hydrochloride (15 g, 132 mmol) in MeOH (130 mL) at 0-5 °C was added TEA (37 mL, 264 mmol). Mixed with a solution of SL-I (20.4 g, 132 mmol) in PCM (50 mL) and stirred at RT for 6 h. The mixture, which contained the intermediate SL-2, was cooled and (Boc) $_2$ O (63.4 g, 290.4 mmol) was added and stirred overnight. MeOH was removed under vacuum. After usual aqueous work-up and chromatographic
10 purification, W-2c was obtained as a colorless oil (14.6 g, 44%).

The above Baker intermediate can also be prepared by the following method;

Step 1: TEA (37 mL, 264 mmol) and a solution of (Boc) $_2$ O (48 g, 220 mmol) in DCM (100 mL) were added to a suspension of cysteamine hydrochloride (20 g, 88.8 mmol) in DCM (300 mL) and stirred at RT for 15 h. The mixture was concentrated and the
15 residue after usual aqueous work-up and chromatographic purification, gave 30 g (96%) of tert-butyl 2-((tert-butoxy)amino)ethyl carbamate as a white solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.43 (s, 9H), 2.78 (t, 4H, J = 6.3 Hz), 3.44 (q, 4H, J = 6.0 Hz), 5.00 (bs, 1H). MS (m/z): 353 [M+H] $^+$, 375.24 (M+Na) $^+$.

Step 2: A solution of 2-mercaptoethanol (1.44 g, 18.5 mmol) in DCM (10 mL) was added
20 to a mixture of tert-butyl 2-((tert-butoxy)amino)ethyl carbamate (5.0 g, 18.2 mmol) and TEA (3.87 mL, 27.3 mmol) in DCM (30 mL) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 2.0 g (56%) of M-2c was obtained. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.43 (s, 9H), 2.79 (t, 2H, J = 6.5 Hz), 2.87 (t, 2H, J = 5.7 Hz), 3.48 (q, 2H, J = 6.3 Hz), 3.58 (t, 2H, J = 5.5 Hz), 4.5
25 (bs, 1H). MS (m/z): 254 [M+H] $^+$, 276.13 [M+Na] $^+$.

Removal of the Boc group of W-2c was accomplished as described in Example 10 to afford the TFA salt, LI-2c.TFA.

Obviously, the linker intermediates W-2b and U-2c can also be synthesized by following the method outlined in Scheme 24.

Example 7

Synthesis of 2-Boc-2-((2-ethoxy-2-oxoethyl)thio)ethyl disulfide (LKW): To an ice-cold solution of LI-2c (9 g, 35.52 mmol) in DCM (80 mL) and TEA (9.9 mL, 70.4 mmol) was added diethylthiosulfonyl chloride (4.2 mL, 53.28 mmol). The reaction mixture was stirred at 0-5 °C for 45 min, then diluted with DCM. After usual aqueous work-up and chromatographic purification, 13.38 g of LI-2d were obtained, which was pure enough for further use. ¹H-NMR (400 MHz, CDCl₃): δ 2.43 (t, 2H, J = 6.4 Hz), 2.98 (t, 2H, 5.7 Hz), 3.05 (s, 3H), 3.35-3.45 (m, 2H), 4.45 (t, 2H, J = 6.7 Hz), 4.78 (br s, 1H).

10 Example 8

Synthesis of 2-Boc-2-((2-ethoxy-2-oxoethyl)thio)ethyl disulfide (LI-2f): To a solution of U-2d (13 & 39.57 mmol) in acetone (100 mL) at RT was added LiBF₄ (6.82 g, 78.54 mmol) and stirred under reflux for 1 h. The reaction mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 8.8 g (78%) of LI-2e.

15 ¹H-NMR (300 MHz, CDCl₃): δ 1.44 (s, 9H), 2.80 (t, 2H, J = 6.32 Hz), 3.06 (t, 2H, J = 6.73 Hz), 3.44 (q, 2H), 3.61 (t, 2H, J = 7.62 Hz), 4.87 (br s, 1H). MS (EI)⁺ m/z: 317 mm⁺.

Example 9

Synthesis of 2-((2-Boc-2-ethoxyethyl)thio)ethyl nitrate (LI-2f): To a solution of XJWe (8 g, 25.3 mmol) in acetone (80 mL) was added AgNO₃ (5.16 g, 30.36 mmol) portionwise and stirred at RT for 1 h in the dark. The mixture was filtered and the filtrate was concentrated. The residue obtained was purified by column chromatography to afford 6.34 g (54%) of U-2f. ¹H-NMR (300 MHz, CDCl₃): δ 1.44 (s, 9H), 2.80 (t, 2H, J = 6.32 Hz), 3.06 (t, 2H, J = 6.73 Hz), 3.44 (q, 2H), 4.70 (t, 2H, J = 7.62 Hz), 4.87 (br s, 1H). MS (EI)⁺ m/z: 299 m/z.

25 The above intermediate was also prepared by the following method: TEA (3.56 g, 35.2 mmol) was added to a solution of cysteine hydrochloride (2g, 17.6 mmol) and U-3b (4.29g, 17.6 mmol) in methanol (25mL) at 0 °C and stirred at RT for 4 h. To the mixture which contained the intermediate thioamine (LI-5) a solution of (Boc-2-ethoxyethyl)amine (7.68 g, 35.2 mmol) and TEA (3.56 & 35.2 mmol) in MeOH (100mL) was added and the mixture was stirred overnight. The reaction mixture was filtered through celite

and evaporated to dryness. The residue was purified by column chromatography to afford 0.380g (7 %) of U-2f.

Example 10

5 Synthesis of 2-((2-((Aminoethyl)thio)ethyl) nitrate.TFA salt (**LI-5/TFA**); To an ice- cold solution of **LUt** (2 g, 6.7 mmol) in DCM (20 mL) was added TFA (5 mL) and stirred at room temperature for 1 h. The mixture was concentrated, the residue was triturated with ether and concentrated to remove traces of TFA and finally dried to afford **UrS-WA**, which was used as such in further reactions.

10 The above linker intermediate M-SJTFA was also synthesized as described below. TEA (3.56 g, 35.2 mmol) was added drop-wise to a solution of cysteoinine hydrochloride (2g, 17.6 mmol) and **LI-3b** (4.29g, 17.6 mmol) in MeOH (25 mL) at 0 °C and stirred at RT for 4 h. The mixture was cooled to 0 °C and a solution of (Boc)₂O (7.68 g, 35.2 mmol) in MeOH (10 mL) was added, followed by TEA (3.56 g, 35.2 mmol), and stirred overnight at RT. The reaction mixture was filtered through celite and the filtrate concentrated. The residue was purified by column chromatography to afford 0.38 g (7.25%) of **UrS**, which was identical (TLC and ¹H-NMR) to that obtained in Example 9. Removal of the Boc group from **LI-2f** to give **LI-5.TFA** was accomplished as described in Example 10.

Example 11

20 Synthesis of methyl 2-((2-hydroxyethylthio)acetate (**LSIIa**); Methyl mercaptoacetate (10.32 g, 97.4 mmol) was added to a solution of **Sir*** (10.0 g, 64.93 mmol) in DCM (150 mL) at RT, followed by TEA (18 mL, 129 mmol) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 2.7 g (22.9 %) of **L3I2a** were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.95 (t, 2H, J = 2.5 Hz), 3.49 (s, 2H), 3.76 (s, 3H), 3.86 (q, 2H, J = 5.64). MS (m/z): **LiZ** [M+H]⁺.

Example 12

30 Synthesis of prodrug **1.CI-PDIO**: This prodrug was synthesized as described in Scheme 11, Method B. Thus, TEA (0.75 mL, 10 mmol) was added to a suspension of cetirizine dihydrochloride (2.0 g, 4.68 mmol) in DMF (50 mL), followed by a solution of **SL-I** (0.72 g, 4.67 mmol), DCC (1.13 g, 5.47 mmol) and DMAP (0.12 g, 1 mmol) and stirred at RT for 15 h. The mixture was concentrated and the residue, after usual aqueous work-

up and chromatographic purification, gave 0.44 g (19%) of I-Cl-PDIO. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.1 O(bs, 4H), 2.5Q (bs, 6H), 2.87 (t, 2H, $J = 6.09$ Hz), 2.94 (t, 2B, $J = 7.32$ Hz), 3.75 (m, 2H), 3.86 (t, 2H, $J = 6.12$ Hz), 4.1B (s, 2H), 4.24 (s, 1H), 4.40 (f, 2H, $J = 5.09$ Hz) aijd 7.22-7.35 (m, 9B). MS (m/z): 527 $[\text{M}+\text{H}]^+$.

5 Example 13

Synthesis of Prodrug I-Cl-PD6: Step 1: To a suspension of aspirin (3 g, 16.65 mmol) in benzene (25 mL) and DMF (2 drops) at 0-5 $^\circ\text{C}$ was added oxalyl chloride (1.7 mL, 19.98 mmol) in benzene (5 mL). The reaction mixture was refluxed at 85 $^\circ\text{C}$ for 2 h, cooled to RT and concentrated to give a yellow oil.

Step 2: The yellow oil was dissolved in benzene (30 mL), silver cyanate (2.99 g, 19.98 mmol) was added and the mixture was refluxed for 1 h in the dark.

Step 3: The reaction mixture was cooled to RT, and a solution of S11 (2.56 g, 16.65 mmol) in benzene (5 mL) was added. The reaction mixture was stored for 2 h, filtered through celite, concentrated and purified by column chromatography to afford 2.24 g

(54%) of I-Cl-PZWF. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 2.12 (s, 3H), 2.83-2.91 (m, 4H), 3.84 (t, $J = 5.9$ Hz, 2H), 4.27 (t, $J = 5.16$ Hz, 2H), 6.20 (f, s, 1H), 7.06 (d, $J = 8.21$ Hz, 1H), 7.19 (t, $J = 7.35$ Hz, 1H), 7.59 (d, $J = 7.24$ Hz, 1H); 7.97 (d, $J = 6.82$ Hz, 1H). MS; m/z 360.06 $[\text{M}+\text{H}]^+$, 377.05 $[\text{M}+\text{H}]^+$, 388.01 $[\text{M}+\text{H}]^+$, 357.98 $[\text{M}+\text{H}]^+$.

Example 14

Synthesis of Prodrug X-Cl-PD11: To a solution of SL-I (7g, 45.45 mmol) and valproic acid (7.85 g, 54.5 mmol) in DCM (80 mL) was added DCC (11.26 g, 54.5 mmol), followed by DMAP (6.65 g, 54.5 mmol), and the resulting suspension was stirred at RT for 18 h. After aqueous work-up and chromatographic purification, 2.82 g (22 %) of X-CX-PD11 was obtained as a colorless oil. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 0.86-0.93 (m, 6H), 1.22-1.29 (m, 8H), 1.32-1.59 (m, 4H), 2.37 (m, 1H), 3.57 (t, 2H, $J = 5.7$ Hz), 4.15 (t, 2H, $J = 6.5$ Hz).

Example 15

Synthesis of prodrug I-Cl-PD13: To a solution of valyromide (5 g, 34.9 mmol) in DCM (50 mL) was added oxalyl chloride (3.7 mL, 41.85 mmol) at 0 $^\circ\text{C}$ and refluxed for 1 h.

The mixture was added to a solution of SL-I (10.76 g, 69.8 mmol) in DCE (50 mL) and stirred overnight at RT. After aqueous work-up and chromatographic purification,

5,01 g (44%) of I-C1-WM3 were obtained as a colorless oil. ^1H NMR (CDCl_3 , 300 MHz): δ 0.89 (t, 6H, $J = 7.21$ Hz), 1.23-1.66 (m, 9H), 2.90 (t, 2H, 5.82 Hz), 2.97 (t, 2H, $J = 6.46$ Hz), 3.90 (t, 2H, $J = 5.82$ KHz), 4.44 (i, 2H, $J = 6.48$ Hz), 7.61 (br s, 1H)

Example 16

- 5 Synthesis of prodrug I-C1-PP14; To a cold solution of diphosgene (0.9 mL, 7.14 mmol) in DCM (5 mL) was added a solution of I-C1-PDU (1 g, 3.57 mmol) and DIPEA (1.9 mL, 10.71 mmol) in DCM (5 mL). The reaction mixture was stirred at RT for 30 min. DCM and excess phosgene were removed under vacuum and the resulting solid was dissolved in DCM (5 mL). To it was added a suspension of mβhaiesulfona pyridine (0.41 g, 4.284 mmol) and DIPEA (1.9 mL, 10.71 mmol) in DCM (5 mL) at 0-5 °C and the mixture was stored overnight at RT. After usual aqueous work-up and chromatographic purification, 1.1 g (77%) of I-C1-PP14 was obtained as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 0.89 (t, 6H, $J = 7.22$ Hz), 1.27-1.63 (m, 9H), 2.34-2.45 (m, 1H), 2.90 (t, 2H, $J = 7.0$ Hz), 2.97 (t, 2H, $J = 6.43$ Hz), 3.30 (s, 3H), 4.36 (t, 2H, $J = 6.99$ Hz), 4.45 (t, 2H, $J = 6.14$ Hz). MS: (ESI) m/z 402 $[\text{M}+\text{H}]^+$, 419 $[\text{M}+\text{NH}_4]^+$, 424 $[\text{M}+\text{Na}]^+$, 440 $[\text{M}+\text{K}]^+$ (ESI-) 401 $[\text{M}-\text{H}]^-$;
- 10
- 15

Example 17

Synthesis of prodrug I-A1-HM;

- This prodrug was synthesized as shown in Scheme 2. Thus, to a solution of amide 1 (18.75 g, 45.86 mmol) in DCM (100 mL) at 0 °C was added triphosgene (4.62 g, 15.59 mmol) followed by TEA (7.71 g, 76.35 mmol) in DCM (10 mL) and stirred at RT for 3 h. To this was added a solution of Lt-U (9.0 g, 48.86 mmol) and TEA (4.63 g, 45.86 mmol) in DCM (10 mL) at 0 °C and stirred at RT for 3 d. The mixture was concentrated and the residue purified by column chromatography to yield 23 g (79.5%) of K-A1-PDI as a white solid (300 MHz, CDCl_3): δ 0.89 (t, 3H, $J = 7.5$ Hz), 2.05 (s, 3H), 2.34 (s, 3H), 2.86-2.94 (m, 4H), 3.43-3.45 (m, 2H), 3.59-3.62 (m, 5H), 4.0-4.35 (m, 4H), 4.30-4.35 (m, 4H), 4.69 (q, 2H, $J = 15$ Hz), 5.20 (b, 1H), 5.38 (s, 1H), 7.01-7.34 (m, 4H). MS (m/z): 631 $[\text{M}+\text{H}]^+$, 653 $[\text{M}+\text{Na}]^+$.
- 20
- 25

Example 18

- 30 Synthesis of prodrug I-A1-PD2: To a solution of I-A1-PDI (23.0 g, 36.45 mmol) in MeOH (250 mL) at 0 °C was added a solution of K_2CO_3 (7.54 g, 54.67 mmol) in water

(55 mL) and stirred for 10 *tain*. The mixture was concentrated and purified by column chromatography to afford 18 g (83.8%) of the prodrug X-A1-PDZ. ¹H-NMR (300 MHz, CDCl₃): δ 1.1* (U 3H, J = 6 Hz), 2.35 (s, 3H), 2.84-2.88 (t, 2H, J « 6 Hz), 2.90-2.94 (t, 2H, J - 6 Hz), 3.44 (bs, 2H), 3.59-3.61 (bs, SH), 3.84-3.91 (m, 2H), 4.0-4.03 (t, 2H, J = 3.11 Hz), 4.33 (bs, 2H), 4.69 (q, 2H, J = 15 Hz), 5.28 (bs, 1H), 5.37 (s, 1H), 7.32-7.36 (m, 4H), MS ES⁺ m/z 589 [M⁺ - 611 (M+Na)].

Example 11

Synthesis of prodrug I-A1-P3: To a suspension of laraotrigine (13.09 g, 51.02 mmol) in toluene (100 mL) at 0 °C was added a solution of W-lyx (5.1 g, 51.02 mmol) in CDCl₃, as described in Scheme 10 (16.27 g, 56.12 mmol) in THF (50 mL) and stirred at 110 °C overnight. The reaction mixture was purified by column chromatography to give 6.0 g (24%) of X-A1-PD3 as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 2.04 (s, 3H), 2.96-3.02 (m, 4H), 4.30-4.35 (m, 2H), 4.45 (t, 2H), 7.38-7.45 (m, 2H), 7.67-7.69 (m, 1H). MS: (ES⁺) m/z 477.9 (M+H)⁺, 499.9 (M+Na)⁺.

Example 20

Synthesis of prodrug I-A1-FD4: To a solution of I-A1-FD3 (2 g, 4.18 mmol) in MeOH (15 mL) and THF (5 mL) at 0 °C was added a solution of K₂CO₃ (0.886 g, 6.276 mmol) in water (5 mL) and stirred at 0 °C for 3 h. After usual aqueous work-up and chromatographic purification, 1.1 g (60%) of I-A1-FD4 was obtained as a white solid, ¹H NMR (DMSO-d₆, 300 MHz): δ 2.75-2.82 (m, 2H), 2.96-3.0 (m, 2H), 3.0 (s, 1H), 3.6 (t, 2H, J « 6.3 Hz), 4.30 (t, 2H, J « 6.5 Hz), 7.38-7.49 (m, 2H), 7.72-7.75 (m, 1H). MS: (ES⁺) m/z 436 (M+H)⁺, 457 (M+Na)⁺.

Example 21

Synthesis of prodrug I-A1-PD5: To a solution of diphosgen (0.99 g, 8.24 mmol) in PCM (3 mL) at 0 °C was added a solution of L3Ka (0.5 g, 2.74 mmol) and Hunig's base (2.39 mL, 13.73 mmol) in DCM (3 mL). The mixture was stirred at 0 °C for 30 min and concentrated to yield the intermediate JLSBa as a light-yellow semi-solid. A solution of a mixture of gabapentin ethyl ester hydrochloride (0.77 g, 3.29 mmol) and Hunig's base (1.7 mL, 9.79 mmol) in DCM (6 mL) was added to the intermediate JLSBa at RT and stirred for 15 h. After usual aqueous work-up and chromatographic purification, 0.34 g (30 %) of I-A1-PD5 were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.26

(t, 3H, $J = 6$ Hz), 1.22-1.51 (m, 10 H), 2.26 (s, 2H), 2.96 (t, 2H, $J = 6$ Hz), 3.1S (d, 2H, $J = 6$ Hz), 3.49 (s, 2H), 3.82 (s, 3H), 4.09 (q, 2H, $J = 6$ Hz), 4.29 (t, 2H, $J = 6$ Hz), 5.39 (bs, 1H). MS: (ES⁺) m/z 408 (M+H)⁺, 430 (M+Na)⁺; (ES⁻) m/z 405 (M-H)⁻.

Example 22

- 5 Synthesis of prodrug I-AlrPDti: To a solution of I-Al-PIrø (10 g, 2.63 mmol) in DCM (3 rat) at RT was added CDI (0.46 g, 2.89 mmol) and stirred for 15 k. A suspension of serine methyl ester hydrochloride (0.61 g, 3.95 mmol) in DCM (4 mL) and TEA (1.1 mL, 7.90 mmol) was added and stirring continued for 15 h. After usual aqueous work-up and chromatographic purification, 0.706 g (51%) of I-Al-FD6 were obtained as a colorless
- 10 oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, $J = 7.1$ Hz), 1.35-1.51 (m, 10H), 2.28 (s, 2H), 2.91-2.98 (m, 4H), 3.16 (t, 2H, $J = 9$ Hz), 3.78 (s, 3H), 3.94-4.38 (m, 9H), 5.5 (bs, 1H), 6.0 (bs, 1H). MS: (ES⁺) m/z 525 (M+H)⁺, 547 (M+Na)⁺. (ES⁻) m/z 523 (M-H)⁻.

Example 23

- Synthesis of prodrug I-Al-FD7: To a solution of I-Al-PD8 (0.6 mg, 0.22 μ mol) in
- 15 DCM (9 mL) at RT was added CDI (40 mg, 0.24 mmol) and stirred for 15 h, after which a solution of dimethyl glutamate (50 mg, 0.45 mmol) and TEA (0.06 mL, 0.45 mmol) was added and stirred for 2 d. After usual aqueous work-up and chromatographic purification, 97 mg (74 %) of I-Al-3PB7 were obtained as a colourless oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, $J = 7.13$ Hz), 1.36-2.5 (m, 16H), 2.93 (s, 4H, $J = 6.46$ Hz), 3.19 (d, 2H, $J = 6.67$), 3.67 (s, 3H), 3.74 (s, 3H), 4.12 (q, 2H, $J = 7.13$ Hz), 4.25-4.44 (m, 5H), 5.4 (bs, 1H), 5.65 (bs, 1H). MS: (ES⁺) m/z 551 (M+H)⁺, 603 (M+Na)⁺; (ES⁻) m/z 571 (M-H)⁻.
- 20

Example 24

- Synthesis of prodrug I-Al-PDJk: To a suspension of gabapentin (10 g, 58.4 mmol) in
- 25 THF (100 mL) at 0 °C was added 1N NaOH (70 mL), followed by (BOC)₂O. The mixture was stirred at RT for 15 h. After washing with diethyl ether (100 mL x 2), the aqueous layer was acidified with solid KHSO₄ and extracted with EtOAc (100 mL x 2). Organic extracts were washed with water (100 mL), dried over Na₂SO₄ and concentrated to afford 10.41 g (68 %) of boc-protected gabapentin as a white solid.
- 30 A Mixture of boc-protected gabapentin (5.0 g, 18.45 mmol) and CDI (3.59 g, 22.14 mmol) in DCM (75 mL) was stored for 15 h. The mixture was concentrated and

dissolved in acetonitrile (50 mL), followed by the addition of 30 % aqueous solution of ammonia (50 mL) and stirred for 1.5 h at RT. After usual aqueous work-up, 4.5 g (90 %) of boc-protected gabapentinamide were obtained as a white solid.

To a solution of boc-protected gabapentinamide (2.59 g, 9.61 mmol) in DCM (12 mL) at 0 °C was added solution of IFA (4 mL) in DCM (4 mL) and stirred for 2.5 h at RT. The mixture was concentrated and dissolved in DCM (20 mL). This was treated successively with Hunig's base (6.7 mL, 38.46 mmol) and LMA (1.45 g, 7.39 mmol), and stirred at RT for 3 h. After usual aqueous work-up and chromatographic purification, 1.19 g (41 %) of I-AL-HR were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.28-1.4 (m, 10H), 2.06 (s, 3H), 2.15 (3, 2H), 2.91 (t, 4H, J = 6.0 Hz), 3.23 (4, 2H, J = 6.0 Hz), 4.2-4.38 (m, 4H), 5.7 (bs, 1H). MS: (ES)⁺ m/z 393 (M+H)⁺; (ES)⁻ m/z 392 (M-H)⁻.

Example 25

Synthesis of prodrug I-AL-PDIO : A mixture of I-AWD8 (1.0 g, 2.63 mmol) and CDI (0.469 g, 2.89 mmol) in DMF (3 mL) was stirred for 12 h, after which N¹,N¹-dimethylethylene-carbodiimide (0.56 mL, 5.26 mmol) and DMAP (0.32 g, 2.63 mmol) was added. The mixture was stirred for 4 h. After usual aqueous work-up and chromatographic purification, 0.763 g (59 %) of I-AL-PDIO were obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 6.0 Hz), 1.28-1.53 (m, 10H), 2.24 (s, 6H), 2.29 (3, 2H, J = 6.0 Hz), 2.42 (t, 2H, J = 6.0 Hz), 2.92 (t, 4H, J = 6.0 Hz), 3.20 (d, 2H, J = 6.0 Hz), 3.26 (q, 4H, J = 6.0 Hz), 4.13 (q, 2H, J = 7.0 Hz), 4.31 (t, 4H, J = 6.0 Hz), 7.26 (bs, 1H). MS: (ES)⁺ m/z 494 (M+H)⁺, 516 (M+Na)⁺; (ES)⁻ m/z 492 (M-H)⁻.

Example 26

Synthesis of prodrug I-AX-PIW1: A mixture of IMA (2.0 g, 15.20 mmol) and CDI (1.98 g, 12.24 mmol) in DCM (12 mL) was stirred for 2 h and concentrated. The residue was dissolved in acetonitrile and a suspension of gabapentin (2.62 g, 15.30 mmol) in saturated NaHCO₃ (15 mL) was added. The mixture was stirred at RT for 15 h. Acetonitrile was removed by distillation and the basic aqueous portion was washed with diethyl ether (100 mL x 2). The aqueous layer was acidified using 2N HCl and extracted with EtOAc (60 mL x 3). The organic layer was concentrated and the residue was purified by chromatographic purification 1.76 g (43 %) of I-AX-PDX1 were obtained as a

colorless oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.27-1.68 (m, 10H), 2.07 (s, 3H), 2.31 (s, 2H), 2.92 (q, 4H, $J = 6.0$ Hz), 3.22 (d, 2H, $J = 9.0$ Hz), 4.31-4.35 (m, 4H), 5.43 (bs, 1H). MS (ES) m/z 392 (M-H).

Example 27

- S Synthesis of prodrug I-A1-PM3: This prodrug was synthesized as shown in Scheme 12, Method B. To a solution of dihydroxyacetone (7.02 g, 58.18 mmol) in DCM (20 mL) at 0 °C was added a solution of M-1a (5.71 g, 29.09 mmol) and Hunig's base (25.3 mL, 145.45 mmol) in DCM (30 mL) and stirred at RT for 40 min. The mixture was concentrated and a mixture of gabapentin ethyl ester hydrochloride (7.546 g, 32 mmol) and Hunig's base (25 mL, 64 mmol) in PCM (50 mL) was added and stirred overnight. Reaction mixture was concentrated and, after usual aqueous work-up and column chromatography, 8.42 g (67 %) of I-AMPD13 were obtained. ^1H NMR (CDCl_3 , 300 MHz): δ 1.22 (t, 3H, $J = 7.3$ Hz), 1.7-1.65 (m, 10H), 2.06 (s, 3H), 2.27 (s, 2H), 2.91 (t, 4H, $J = 6.6$ Hz), 3.19 (d, 2H, $J = 6.7$ Hz), 4.08 - 4.15 (q, 2H, $J = 7.1$ Hz), 4.27-4.34 (q, 4H, $J = 6.4$ Hz), 5.4 (bs, 1H). MS (ESI) m/z 422 [M+H] $^+$, 444 [M+H] $^+$.
- 10
- 15

Example 28

- Synthesis of prodrug I-A1-FDf: To an ice-cold solution of I-A1-PD13 (5.0 g, 18.98 mmol) in MeOH (30 mL) was added a solution of K_2CO_3 (5.24 g, 37.96 mmol) in water (38 mL). After 15 min, the mixture was concentrated. After usual aqueous work-up, 5.0 g (69 %) of I-A1-PDS were obtained. ^1H NMR (CDCl_3 , 300 MHz): δ 1.25 (t, 3H, $J = 7.11$ Hz), 1.30-1.71 (m, 10H), 2.87-2.94 (b, 4H), 2.27 (s, 2H), 3.18 (d, 2H, $J = 6.6$ Hz), 3.87 (t, 2H, $J = 5.7$ Hz), 4.09-4.16 (q, 2H, $J = 7.12$ Hz), 4.31 (t, 2H, $J = 6.51$ Hz), 5.44 (bs, 1H). MS (ESI) m/z 380 [M+H] $^+$, 402 [M+H] $^+$.
- 20

Example 29

- Synthesis of prodrug I-A1-PB12: To a solution of dihydroxyacetone (7.02 g, 58.18 mmol) in DCM (20 mL) at 0 °C was added a solution of I-A1-H8 (4 g, 10.54 mmol) and Hunig's base (5.5 mL, 31.62 mmol) in DCM (30 mL). The mixture was stirred at RT for 40 min, cooled to 0-5 °C, and dry ammonia gas was passed through it for 30 min. Reaction mixture was concentrated and, after usual aqueous work-up, 5.3 g (91 %) of I-AUVO 12 were obtained. ^1H NMR (CDCl_3 , 300 MHz): δ 1.23 (t, 3H, $J = 7.4$ Hz), 1.27-1.79 (m, 10H), 2.06 (s, 3H), 2.27 (s, 2H), 2.91 (t, 4H, $J = 6.6$ Hz), 3.19 (d, 2H, $J = 6.7$ Hz), 4.08 - 4.15 (q, 2H, $J = 7.1$ Hz), 4.27-4.34 (q, 4H, $J = 6.4$ Hz), 5.4 (bs, 1H). MS (ESI) m/z 422 [M+H] $^+$, 444 [M+H] $^+$.
- 25
- 30

1OH), 2-2S (s, 2H), 2.91-3.03 (ra, 4H), 3.19 (d, 2H, J = 6.7 Hz), 4.12 (q, 2H, J = 7.1 Hz), 4.31 (t, 4H, J = 6.4 Hz), 5.4 (t, 1H, J = 6.0 Hz). MS; m/z 423 [WK], 446 [M+Na].

Example 30

Synthesis of prodrug I-A1-PD14: Ethyl chloroformate (OM g, 7.9 mmol) was added to a solution of 3-carbamoylroethyl-5-meHiylhexanoic acid (M. S. HbeJcstra *et al*, *Org. Proc. Res. Rev.*, 1997, U26-38) (1.0 g, 53 mmol) in THF (6 mL) at -10 °C, followed by TEA (2.4 mL, 17.0 mmol) and the mixture was stirred at -10 °C for 30 min. A solution of NaN₃ (1.73 g, 26.6 mmol) in water (10 mL) was added and stirred for 2 h at -10 °C. The reaction mixture was brought to RT and extracted with EtOAc (3 x 25 mL), washed with water (2 x 25 mL), dried over Na₂SO₄ and concentrated. Toluene (20 mL) was added to the residue and refluxed for 6 h. After cooling to RT, a solution of SL-I (825 mg, 53 mmol) in DCM (10 mL) was added and stirred at RT for 14 h. After usual aqueous work-up and chromatographic purification, 315 mg (17 %) of I-A1-PD14 were obtained as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 0.89-0.95 (ra, 6H), 1.25-1.29 (m, 2H), 1.62-1.71 (m, 1H), 2.04-2.1 (no, t, 1H), 2.38 (d, J = 5.2 Hz, 2H), 2.87-2.95 (ro, 4H), 3.05-3.36 (m, 2H), 3.88 (f, J = 5.7 Hz, 2H), 4.34 (t, J = 6.2 Hz, 2H), 5.06 (br s, 1H). MS; m/z 338 [M]⁺.

Example 31

Synthesis of prodrug I-A1-PD14: To a solution of I-A1-PD4 (0.350 g, 0.802 mmol) in DMP (3 mL) at RT was added CPI (0.195 g, 1.204 mmol) and stirred at RT for 3 h. This mixture was added to a suspension of methanesulphonamide (0.304 g, 3.2 mmol) in DMF (4 mL) and NaH (0.53 g, 3.2 mmol) at 0 °C and stirred at RT for 4 h. The reaction was quenched with ice and, after usual aqueous work-up and chromatographic purification, 0.12 g (26%) of I-A1-PD14 were obtained as a white solid. ³H NMR (CDCl₃ + CD₃OD, 300 MHz): δ 2.53-2.90 (m, 4H), 3.10 (s, 3H), 4.26-4.36 (m, 4H), 7.19-7.28 (m, 2H), 7.48-7.51 (m, 1H). MS: (ES⁺) m/z 556.96 (M+B)⁺, 578.92 (M+Na)⁺.

Example 32

Synthesis of prodrug X-A1-PMS: CDI (4 g, 24.7 mmol) was added to a solution of M-2c (4 g, 15.5 mmol) in THF (30 mL) and stirred at RT for 2 h. Then a solution of gabapentin (4 g, 23.4 mmol) in 20 % NaHCO₃ solution (10 mL) was added and stirred overnight at RT. The reaction mixture was neutralized with 0.5N HCl (pH ~ 4), extracted

with EtOAc (4 x 40 ml), dried over Na₂SO₄, concentrated and purified by column chromatography to afford 4.7 g (66 %) of I-S12-PD2 as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.45-1.49 (br s, 19H), 2.35 (s, 2H), 2.80-2.97 (m, 4H), 3.24 (d, J = 5.7 Hz, 2H), 3.46 (an, 2H), 4.33 (t, J = 5.7 Hz, 2H), 5.0 (br s, 1H), 5.71 (br s, 1H). MS: (m/z) [ES]⁺ 449.1 (M-Hf; [ES]⁺ 451.2 [M+Hf,

EtOAc saturated with HCl gas (5mL) was added to I-S12-PD2 (0.55 g, 1.22 mmol) and stored at RT for 10 h. Solvent was removed under reduced pressure and purified by preparative HPLC to give 425 mg (90 %) of I-A1-PD18 as a colorless liquid. ¹H NMR (300 MHz, CD₃OD): δ 1.52 (br s, 10H), 2.4 (s, 2H), 2.98-3.07 (m, 4H), 3.27-3.34 (ra, 2H), 3.61 (s, 2H), 4.5 (t, J = 6.0 Hz, 2H). MS: [ES]⁺ m/z 351.0 [M+Hf, Example 33

Synthesis of prodrug I-A2-PD1: To a solution of levetiracetam (LO g, 5.87 mmol) in DCE (20 mL) and DCM (4 mL) was added oxalyl chloride (0.61 mL, 7.05 mmol), and heated at 70 °C for 8h. Reaction mixture was cooled and added to a solution of SL-X (1.81 g, 7.5 mmol) in DCM (15 mL) and stirred at RT overnight. After chromatographic purification, 143 g (41%) of I-A2-PD1 were obtained. ¹H NMR (CDCl₃, 300 MHz): δ (ppm): 0.87 (t, J = 7.3 Hz, 3H), 1.84-2.04 (m, 4H), 2.41 (t, J = 6.9 Hz, m), 2.69 (bs, 1H), 2.87-2.95 (m, 4H), 3.02-3.11 (m, 1H), 3.65-3.75 (m, 1H), 3.85-3.95 (m, 2H), 4.06-4.12 (m, 1H), 4.34-4.41 (m, 2H), 8.69 (bs, 1H). MS: (ES⁺): m/z 351.0 [M+Hf; 372.9 (M+Na)⁺.

Example 34

Synthesis of prodrug I-A3-PD1: To a solution of I-S13-JPP1 (which was synthesized as described in Example 37, Step 2) (215 mg, 0.292 mmol) and triisopropylsilane (60 μL) in 0.75 mL of DCM was added 20 % TFA in BCM (0.5 mL) and stirred at RT for 90 min. The mixture was concentrated and the residue purified by column chromatography to give 55 mg (46%) of I-A3-PD1. ¹H-NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.85-2.92 (m, 4H), 3.87 (t, 2H, J = 4.5 Hz), 4.37 (t, 2H, J = 6.0 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J = 3.0 Hz). MS (m/z): 493 [M-HT, 517 (M+Na)⁺.

Example 35

Synthesis of prodrugs I-A3-PP3a and I-A3-FJ3fc Step 1: PSC 10 (0.824 mmol) and TEA (0.230 mL, 1.64 mmol) were added to a solution of methyl 2-

hydroxyethyl)dithioacetate (100mg, 0.549 mmol) in acetonitrile (1 mL) at 0 °C and stirred at RT for 3h. The mixture was concentrated and the residue dissolved in DCM. Usual aqueous work-up and chromatographic purification gave the crude intermediate.

Step 2: TEA (24mg, 0.236 mmol) and DMAP (13 mg) were added to a mixture of valdecoxib (62mg, 0.195 mmol) and the product obtained from step 1 above in THF (1 mL) and stirred at RT for 3 h. The mixture was concentrated and the residue dissolved in EtOAc. After usual aqueous work-up and chromatographic purification, 53 mg (52%) of 1-A3-P03a obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.51 (s, 3H), 2.97 (t, 2H, J = 6.0 Hz), 3.48 (s, 2H), 3.76 (s, 3H), 4.37 (t, 2H, J = 6.0 Hz), 7.33-7.40 (m, 1B), 8.03-8.12 (m, 2H), MS (m/z): 521 [M-H]⁺.

Step 3: The above material was converted to the corresponding mono-, and/or di-sodium salt for **I-A3-FD3b** by using standard methods. Thus, to a cold solution of the above compound (150 mg, 0.287 mmol) in THF (1 mL) was added 1M LiOH solution (28 mg in 1mL water) and stirred overnight at RT. The mixture was concentrated, the residue diluted with water, acidified with 1M HCl (~3 mL, pH ~3) and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 20 mg (13%) of product were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.49 (s, 3H), 2.70-2.89 (m, 4H), 4.23-4.33 (m, 2H), 7.28-7.38 (m, 7H), 8.01-8.03 (m, 2H).

Example 36

20 Synthesis of prodrug **I-A3-FD4**: This prodrug was synthesized as described in Sclrønes 13, Method B.

Step 1: Synthesis of intermediate LI-8;

CDI (1.65 & 10.19 mmol) was added to a solution of 3Ut-Ia (2.0 g > 10.19 mmol) in DMF (10 mL) and stirred at RT for 3 h. N,N-Dimethylethylcarbamate (1.2 mL, 11.12 mmol) was added and stirred for 2 h. The mixture was concentrated and the residue taken up in EtOAc. After usual aqueous work-up and chromatographic purification, 1.3 g (41%) U-S were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.07 (s, 3H), 2.31 (bs, 6H), 2.51 (t, 2H, J = 6.0 Hz), 2.91 (t, 4H, J = 6.0 Hz), 3.31 (q, 2H, J = 6.0 Hz), 4.28-4.34 (m, 4H), 5.52 (broad IH). MS (m/z): 333 [M+Na].

30 Step 2: Synthesis of intermediate **LI-9**: To a solution of LI-8 (13 > 18 mmol) in MeOH (7 mL) was added a 1.25M solution of K₂CO₃ (5 mL) and stirred at RT for 1h.

The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up, 1.02 g (91%) of product were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.29 (s, 6H), 2.54 (t, 2H, J = 6.0 Hz), 2.86-2.99 (m, 4H), 3.33 (q, 2H, J = 5.0 Hz), 3.86 (t, 2H, J = 6.0 Hz), 4.31 (t, 2H, J = 6.0 Hz), 5.71 (bs, 1H), MS (m/z): 269 [M+H]⁺. This product was used as such in the next step.

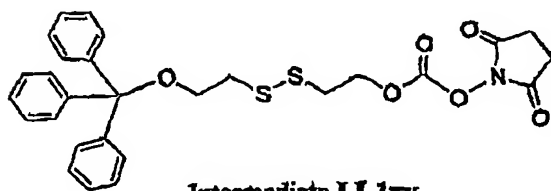
Step 3: Synthesis of intermediate LMO; A solution of I-9 (1.02 g, 3.80 mmol) in acetonitrile (10 mL) was added to a cold solution of DSC (1.46 g, 5.0 mmol) in acetonitrile (50 mL) followed by TEA (1.58 mL, 11.40 mmol), and stirred overnight at RT. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up, 1.33 g (85%) of W-10 were obtained.

Step 4: Synthesis of I-A3-PD4: TEA (0.94 mL, 9 mmol) and DMAP (73 mg, 0.6 mmol) were added to a solution of W-10 (1.33 g, 3.24 mmol) and valdecoxib (364 mg, 1.16 mmol) in THF (6 mL) and stirred at RT for 5 d. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up and chromatographic purification, 177 mg (12 %) of LMO were obtained. ¹H-NMR (300 MHz, CDCl₃): δ 2.46 (s, 3H), 2.85-2.95 (m, 4H), 3.28 (t, 2H, J = 6.0 Hz), 3.65 (t, 2H, J = 3.0 Hz), 4.22-4.28 (m, 4H), 7.22-7.41 (m, 7H), 7.94 (d, 2H, J = 9.0 Hz). MS (m/z): 609 [M+H]⁺. This product was converted to water-soluble hydrochloride salt form using standard methods.

Example 37

Synthesis of prodrug I-A3-PD5: This prodrug was synthesized as shown in Scheme 13. Method B.-

Step 1: Synthesis of prodrug intermediate LHs: -



Intermediate LI-1xy

5 A solution of *U-U* (1.0 g, 2.52 mmol) in acetonitrile (10 mL) was added to a solution of DSC (0.96 g, 3.78 mmol) in acetonitrile (20 mL) and stirred for 10 min. After cooling to 0 °C, TBA (1 mL, 7.57 mmol) was added and stirred at RT for 3.5 h. The solution was concentrated and the residue was taken up in DCM. After usual aqueous work-up, the crude product obtained was used as such in the next step.

10 Step 2: Synthesis of prodrug intermediate I-S13-PD1: A mixture of the above intermediate (2.5 mL) and valdecoxib (280 mg, 0.892 mmol), DMAP (56 mg, 0.5 mmol) and TEA (ISO μ L, 1.06 mmol) in THF (5 mL) was stirred at RT for 4.5 d. The mixture was concentrated and the residue dissolved in EtOAc. After usual aqueous work-up and chromatographic purification, 354 mg (54 %) of I-SU-H was obtained. ¹H-NMR (300 MHz, CDCl₃): 8.247 (s, 3H), 3.32-3.41 (m, 4H), 4.28 (t, 2H, J = 6.0 Hz), 4.47 (t, 2H, J = 6.0 Hz), 7.20-7.61 (m, 22H), 8.00 (d, 2H, J = 9.0 Hz). MS (m/z): 736 [M-H]⁺.

15 Step 3: Synthesis of intermediate I-A3-PD1: To a solution of I-S13-PD1 (215 mg, 0.292 mmol) and isopropyl alcohol (60 μ L) in 0.75 mL of DCM was added 20% TPA in DCM (0.5 mL) and stirred at RT for 90 min. The mixture was concentrated and the residue purified by column chromatography to give 65 mg (46%) of I-A3-PD1. ¹H-NMR (300 MHz, CDCl₃): 8.251 (s, 3H), 2.85-2.92 (m, 4H), 3.87 (t, 2H, J = 4.5 Hz), 4.37 (t, 2H, J = 4.5 Hz), 7.25-7.43 (m, 7H), 8.01 (d, 2H, J = 3.0 Hz). MS (m/z): 493 [M-H]⁺; 517 [M+Na]⁺.

20 Step 4: Synthesis of I-A3-PD1-Me-ester: CUI (40 mg, 0.243 mmol) was added to a solution of I-A3-PD1 (100 mg, 0.202 mmol) in DMF (0.5 mL) and stirred at RT for 2.5 h. To this were added a solution of dimethyl glutarate (53 mg, 0.303 mmol) in DMF (0.5 mL) and DMAE (37 mg, 0.303 mmol) and stirred overnight at RT. The mixture was dissolved in EtOAc and, after usual aqueous work-up and chromatographic purification, 110 mg (78%) of I-A3-PD1-Me-ester was obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.71-1.91 (m, 2H), 2.38-2.42 (m, 2H), 2.44 (s, 3H), 2.84-2.95 (m, 4H), 3.66 (s, 3H), 3.67 (s, 3H), 4.33-4.34 (m, 4H), 4.43-4.52 (m, 1H), 7.31-7.41 (m, 7H), 8.02 (d, 2H, J = 9.0 Hz). MS (m/z): 694 [M-H]⁺.

30 Step 5: Synthesis of prodrug I-A3-PD1-Me-ester: IK titi on hydroxide (1.2 mL, 1.2 mmol) was added to a solution of I-A3-PD1-Me-ester (100 mg, 0.144 mmol) in THF (0.4 mL) at 0 °C and the mixture allowed to attain ambient temperature. After 30 min, the mixture was

concentrated and the residue diluted with water. Acidification with 1N HCl, followed by extraction with EtOAc, usual aqueous work-up and chromatographic purification gave 26 mg (26%) of I-A3-PD5, $^1\text{H-NMR}$ (300 MHz, CDCl_3); δ 2.197 (m, 1H), 2.05-2.13 (m, 1H), 2.30-2.40 (m, 2H), 2.48 (s, 3H), 2.84 - 2.94 (m, 4H), 4.06 - 4.08 (m, 1H), 4.15 ~ 4.22 (m, 4H), 7.30 (d, 2H, $J \approx 9$ Hz), 7.35 - 7.41 (m, 5H), 7.92 (d, 2H, $J = 9.0$ Hz). MS (m/z): 666 [M-H] $^-$.

E. Example 38

Synthesis of prodrug H-1-HH: This prodrug was synthesized as shown in Scheme 14, Table 1.

10 Step 1: A solution of metronidazole (5.0 g, 29.22 mmol) and CDI (5.21 g, 32.2 mmol) in DCM (100 mL) was stirred overnight at RT. After usual aqueous work-up, 7.32 g of the 2DME of metronidazole were obtained, which was used as such in the next step.

Step 2: A solution of the imidazole of metronidazole (7.32 g) in OMF (30 mL) was added to a solution of S1 (6.39 g, 41.43 mmol) in DMF (10 mL) and stirred at 60 °C for 2.5 h. The mixture was concentrated and the residue was taken up in DCM. After usual aqueous work-up and chromatographic purification, 6.32 g (65%) of I-H1-PD1 were obtained. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.15 (bs, 1H), 2.52 (s, 3H), 2.83-2.92 (m, 4H), 3.84-3.92 (m, 2H), 4.34 (t, 2H, $J = 6.0$ Hz), 4.51 (t, 2H, $J = 3.0$ Hz), 4.53-4.62 (m, 2H), 7.0 (s, 1H).

20 Example 39

Synthesis of I-HJ-PD14: This prodrug was synthesized as described in Scheme 14, Method C. Thus, TEA (0.915 mL, 6.36 mmol) and DMAP (cat) were added to a solution of U-2C.TFA (541 mg, 3.94 mmol) and the imidazole of metronidazole (synthesis described in Example 114) (870 mg, 3.28 mmol) in DMF (2 mL) and the mixture was heated at 60 °C for 3.5 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 546 mg (48%) of I-HI-PDH. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.48 (s, 3H), 2.56-2.66 (m, 4H), 3.46 (q, 2H, $J = 6.0$ Hz), 3.87 (t, 2H, $J \approx 6.0$ Hz), 4.41 (t, 2H, $J \approx 6.0$ Hz), 4.57 (t, 2H, $J \approx 4.5$ Hz), 7.90 (s, 1H). MS (m/z): 351 [M-H] $^+$.

30 Example 40

Synthesis of prodrug **I-H1-PD2**: This prodrug was synthesized as described in Scheme 14, Method C. Thus, CDI (180 mg, 1.1 mmol) was added to a solution of I-BUPD14 (350 mg, 1.0 mmol) in DMF (2 mL) and stirred at RT for 4 h. *N,N*-Diniethylethylenediamine (88 mg, 1.0 mmol) was added and stirred for 3 h. The mixture was concentrated and the residue purified by column chromatography to afford 175 mg (38%) of HW-P02. ¹H-NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H), 2.49 (s, 6H), 2.51-2.55 (m, 2H), 2.81 (t, 2H, J = 6.0 Hz), 2.89 (t, 2H, J = 6.0 Hz), 3.27-3.33 (m, 2H), 3.46 (q, 2H, J = 6.0 Hz), 4.29 (t, 2H, J = 6.0 Hz), 4.40 (t, 2H, J = 4.5 Hz), 4.57 (t, 2H, J = 4.5 Hz), 5.55 (bs, 1H), 7.94 (s, 1H). MS (m/z): 465 [M+H]⁺. This product was converted to water-soluble hydrochloride salt form using a standard method.

Example 41

Synthesis of prodrug **I-H1-IPDS**: This prodrug was synthesized as described in Scheme 14, Method A.

Step 1: Synthesis of Intermediate **I-S14-PD1**: A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.6 g, 2.98 mmol) in acetonitrile (10 mL) was added to a solution of 2'-deoxy-2'-fluoroadenosine (0.8 g, 3.74 mmol) in acetonitrile (20 mL) at RT, followed by DMAP (0.914 g, 7.45 mmol) and stirred for 24 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, gave 0.62 g (79%) of intermediate **I-S14-PD1**. ¹H-NMR (300 MHz, CDCl₃): δ 1.95 (s, 3H), 2.35-2.45 (m, 2H), 2.75 (t, 2H, J = 6.6 Hz), 2.87 (t, 2H, J = 6.33 Hz), 3.35 (t, 2H, J = 6.33 Hz), 4.05 (dd, 1H), 4.25 (m, 1H), 4.35 - 4.41 (m, 4H), 6.20 (t, 1H, J = 6.16), 7.21-7.33 (m, 9H), 7.42-7.48 (m, 6H) and 8.49 (s, 1H). MS (m/z): 712 [M+Na]⁺.

Step 2: Synthesis of **I-H1-FDS**: To a solution of **I-S14-PD1** in DCM (15 mL) were added triisopropylsilane (0.446 mL, 2.17 mmol), followed by 10% TFA in DCM (15 mL) and stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography to afford 0.8 g (70%) of prodrug **X-H1-PD5**. ¹H-NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H), 2.30 (bs, 1H), 2.41-2.48 (m, 2H), 2.88 (t, 2H, J = 6.1 Hz), 2.96 & 2.98 (t, 2H, J = 6.6 Hz), 3.88 (t, 2H, J = 5.8 Hz), 4.05 (dd, 1H), 4.29 (m, 1H), 4.30-4.48 (m, 4H), 6.18 (t, 1H, J = 6.3 Hz), 7.34 (s, 1H), 7.42-7.48 (m, 6H). MS (m/z): 448 [M+H]⁺, 470 [M+Na]⁺.

Example 42

Synthesis of prodrug I-S22-PIM: This prodrug was synthesized in two steps as shown in Scheme¹.

Step 1: To a solution of diphosgene (0.35 mL, 2.93 mmol) in DCM (5 mL) was added a solution of U-Id (0.404 g, 1.75 mmol), Hünig's base (0.765 mL, 4.39 mmol) and the resulting mixture was stored at RT for 45 min. The mixture was concentrated, the residue dissolved in DCM (5 mL), cooled in an ice-bath and treated with a solution of pyridine (500 mg, 0.585 mmol), Hünig's base (0.765 mL, 4.39 mmol) and DMAP (cat.) in DCM (5 mL) over 5 min and the resulting mixture was stirred at RT for 2 h. The mixture was purified by column chromatography to give 519 mg (78%) of the protected intermediate S22-12 as an off-white solid, ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.28 (s, 3H), 1.68 (s, 3H), 2.04 (s, 3H), 2.23 (s, 3H), 2.37 - 2.45 (m, 2H), 2.46 (s, 3H), 2.50 - 2.52 (ax, 2H), 2.90 - 2.95 (m, 4H), 3.82 (d, 1H, J = 7.0 Hz), 4.05 (s, 2H), 4.21 (d, 1H, J = 8.5 Hz), 4.32 (d, 1H, J = 8.0 Hz), 4.40 - 4.42 (m, 5H), 4.97 (d, 1H, J = 9.5 Hz), 5.29 (s, 1H), 5.43 (d, 1H, J = 2.5 Hz), 5.69 (d, 1H, J = 10 Hz), 6.00 (dd, 1H, J = 9.5 Hz, 2.5 Hz), 6.26-6.29 (m, 2H), 7.02 (d, 1H, J = 9.5 Hz), 7.38 - 7.61 (m, 1H), 7.75 (d, 2H, J = 7.5 Hz), 8.15 (d, 2H, J = 7.5 Hz).

Step 2: To an ice-cold solution of S22-12 (60 mg, 0.0532 mmol) in MeOH (1 mL) was added 2 drops of methanol saturated with ammonia gas and the resulting mixture was stirred for 1 h. The reaction mixture was purified by column chromatography to give 38 mg (69%) of I-S22-WM as an off white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.23 (s, 3H), 2.35 - 2.42 (m, 2H), 2.46 (s, 3H), 2.50 - 2.58 (m, 2H), 2.84 (t, 2H, J = 5.4 Hz), 2.94 (t, 2H, J = 6.5 Hz), 3.82 (t, 3H, J = 6.0 Hz), 4.20 (d, 1H, J = 8.5 Hz), 4.31 (d, 1H, J = 8.5 Hz), 4.35 - 4.41 (m, 3H), 4.97 (d, 1H, J = 7.5 Hz), 5.44 (d, 1H, J = 2.5 Hz), 5.69 (d, 1H, 7.0 Hz), 6.0 (dd, 1H, J = 9.25 Hz, 2.25 Hz), 6.22-6.29 (m, 2H), 7.08 (d, 1H, J = 9.5 Hz), 7.36-7.60 (m, 1H), 7.78 (d, 2H, J = 7.5 Hz), 8.14 (d, 2H, J = 7.5 Hz).

Example 43

Synthesis of prodrug I-S22-PD2t To a solution of I-S22-FD1 (38 mg, 0.0367 mmol) in acetonitrile (0.6 mL) was added succinic anhydride (5 mg, 0.044 mmol) and DMAP (cat). The resulting mixture was stirred overnight at RT and purified by column

- chromatography to give 12 mg (29%) of prodrug **I-S22-PD2** as an off white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.14 (s, 3H), 1.28 (s, 3H), 1.68 (s, 3H), 1.91 (s, 3H), 2.22 (s, 3H), 2.36 - 2.41 (m, 1H), 2.49 (s, 3H), 2.57 - 2.63 (m, 5H), 2.86 - 2.89 (m, 2H), 2.93 (t, 2H, J = 6.5 Hz), 3.79 (d, 1H, J = 7.0 Hz), 4.20 - 4.44 (ra, 7H), 4.98 (4 1H, J = 8.0 Hz), 5.53 (d, 1H, 3.0 Hz), 5.69 (d, 1H, J = 7.0 Hz), 6.02 (dd, 1H, J = 9.5 Hz, J = 3.0 Hz), 6.26, 6.29 (ra, 2H), 7.20 (d, 1H, J = 9.0 Hz), 7.33 - 7.62 (m, 4H), 7.74 (d, 2H, J = 7.5 Hz), 8.14 (d, 2H, J = 7.5 Hz). MS (ES⁺) m/z 1134.44 [M+H]⁺, 1156.56 [M+Na]⁺.
- Water solubility:** Paditax **I** and its prodrug **I-1522-I*302** (2 mg each) were suspended in 1 mL water or PBS-buffer (pH 7.4). The suspensions were sonicated for 15 min and centrifuged (13,000 g) for 10 min. The supernatant was analyzed using HPLC.
- HPLC: Waters RP18 column (150 x 3.9 mm, X-Tra); DAD-HP Agilent (Model 1100); eluent: CH₃CN/H₂O (gradient 0-100% acetonitrile in 45 min). The UV-detector was set at 210 nm. The concentrations were determined by measuring the relative area of paclitaxel or **I-S22-PD2**. It was observed that the solubility of **I-S22-PD2** was 20 times more than that of paclitaxel. (i.e., 0.2 mg/mL).

The following double/mutual prodrugs (Examples 44 - 80) were synthesized by the methods depicted in Schemes 17-21, using appropriate therapeutic agents and obvious modifications:

Example 44

- 20** Synthesis of mutual prodrug of desloratidine and pseudoephedrine (**I-AA-MPDI**):
- This mutual prodrug was synthesized as depicted in Scheme 21. The compound **I-AA-MPDI** was obtained as a colorless gum. ¹H-NMR (300 MHz, CDCl₃): δ 1.00 (d, 3H, J = 6.9, Hz), 2.27-2.51 (m, 4H), 2.74-2.97 (m, 9H), 3.25-3.41 (m, 4H), 3.79 (bs, 2H), 4.28-4.30 (m, 4H), 4.57 (m, 1H), 7.04-7.44 (m, 9H), 8.26-8.33 (m, 2H). MS (m/z): 682 [M+H]⁺.

Example 45

Synthesis of mutual prodrug of amlodipine and lisinopril (**I-AA-MFDJ**):

Step 1: Synthesis of diethyl ester of lisinopril:

- 30** To a suspension of lisinopril (10.0 g, 22.62 mmol) in ethanol (150 mL) was added SOCl₂ (4.95 mL, 67.94 mmol) and refluxed for 1.5 h. An additional 1 mL of SOCl₂ was added to the mixture every hour for 4 h. The mixture was concentrated and azeotroped with

benzene. The resulting hydrochloride was basified with saturated NaHCO_3 and extracted with EtOAc. Usual aqueous work-up gave 12.86 g of Usinoprtt diethyl ester, which was used without purification. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.23-1.64 (m, 10H), 1.89-2.3 (BR, 6H), 2.63-2.66 (m, 2H), 2.80 (bs, 2H), 3.19 (t, 2H, $J = 7.5$ Hz), 3.364.59 (m, 6H), 4.12-4.19 (m, 4H), 4.4-4.5 (m, 1H), 7.14-7.28 (m, 5H). MS [m/z]: 462.4 [M+Hf].

Step 2; Synthesis of I-AA-MPP2: CDI (1.23 g, 7.64 mmol) was added to a solution of I-A1-PD2 (Example 18) (3.0 g, 5.09 mmol) in DMF (10 mL) and stirred RT for 3.5 h. A solution of Hsinopril diethyl ester (2.34 g, 5.09 mmol) in DMF (5 mL) was added and stirred at 65°C for 8 h. The reaction was quenched with brine and taken up in EtOAc. After usual aqueous work-up and chromatographic purification, 2.5 g (45%) of J-AA-MP02 were obtained. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.17 (t, 3H, $J = 7.5$ Hz), 1.24-1.30 (m, 7H), 1.45-1.80 (m, 7H), 1.90-2.30 (m, 7H), 2.36 (s, 3H), 2.70 (bs, 2H), 2.89-2.95 (m, 4H), 3.10-3.20 (bs, 3H), 3.40-3.70 (m, 9H), 4.00-4.40 (m, 10H), 4.47-4.53 (m, 1H), 4.68-4.73 (q, 2H, $J = 13$ Hz), 5.30 (bs, 1H), 5.39 (s, 1H), 5.65 (d, 1H), 7.15-7.36 (m, 9H). MS (m/z): 1076 [M+Hf], 1098 [M+Naf].

Example 46

Synthesis of mutual prodrug of amlodipine and Losartan (I-AA-MP00a);

This mutual prodrug was synthesized as described in Example 34, with obvious modifications, using the appropriate amino containing therapeutic agents. The product I-AA-MP00a was obtained as a cream color solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.86 (t, 3H, $J = 6.6$ Hz), 1.16 (t, 3H, $J = 7.1$ Hz), 1.31 (m, 2H), 1.60 (m, 2H), 2.31 (s, 3H), 2.48 (t, 2H, $J = 7.9$ Hz), 2.804.92 (m, 4H), 3.40 (m, 4H), 3.56 (s, 3H), 4.01 (m, 2H), 4.32 (m, 4H), 4.68 (q, 2H, $J = 6.5$ Hz), 5.00 (s, 2H), 5.14 (s, 2H), 5.37 (s, 1H), 6.90 (d, 1H, $J = 7.8$ Hz), 7.02-7.22 (m, 5H), 7.33-7.43 (m, 3H), 7.50-7.60 (m, 2H). MS (m/z): 1037 [M-H]⁺.

Example 47

Synthesis of mutual prodrug of celecoxib and valdecoxib (U-AA-MPD4):

This mutual prodrug was synthesized by reacting the imidazoline intermediate of I-A3-PPJ with valdecoxib according to method described in Scheme 17 with appropriate modifications. This mutual prodrug I-AA-MPD4 was obtained as a white solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.16 (s, 3H), 2.29 (s, 3H), 2.71 (bs, 4H), 4.14 (bs, 4H), 6.69 (s, 2H), 7.02-7.33 (m, 14H), 7.97 (d, 3H, $J = 9.0$ Hz). MS (m/z): 900 (M-H)⁺.

Example 48

Synthesis of double prodrug of valdecoxib (I-AA-MPD5):

- 5 This double prodrug was synthesized by reacting *hAS-TDI* and valdecoxib using the method B described in Scheme 13. The double prodrug I-AA-MPD5 was obtained as an off white solid, ¹H-NMR (300 MHz, CDCl₃): δ 2.40 (s, 6H), 2.82 (bs, 4H), 4.20 (bs, 4H), 7.20-7.35 (m, 14H), 7.97 (d, 4H, J = 9.0 Hz). MS (m/z): 833 [M-H]⁻.

Example 49

Synthesis of double prodrug of valdecoxib (I-AA-MPD8a):

- 10 This double prodrug was synthesized using succinic anhydride and valdecoxib according to method B described in Scheme 13 with appropriate modifications. This double prodrug I-AA-MPD8a was obtained as an off-white solid. ¹H-NMR (300 MHz, CDCl₃): δ 2.46 (s, 6H), 2.58 (s, 4H), 7.25-7.37 (m, 14H), 7.95 (d, 2H, J = 9.0 Hz). MS (m/z): 709 [M-H]⁻.

Example 50

- 15 Synthesis of double prodrug of valdecoxib (I-AA-MPD8b):

This double prodrug was synthesized using succinic anhydride and valdecoxib according to method B described in Scheme 13 with appropriate modifications. This double prodrug I-AA-MPD8b was obtained as a colorless gum. ¹H-NMR (300 MHz, CDCl₃ + CD₃OD): δ 1.68-1.74 (m, 2H), 2.15 (t, 4H, J = 4.5 Hz), 2.38 (s, 6H), 7.01 (bs, 1H), 7.17-7.30 (m, 14H), 7.50 (bs, 1H), 7.88 (d, 4H, J = 8.58 Hz). MS (m/z): 723 [M-H]⁻.

Example 51

Synthesis of double prodrug of olanzapine and fluoxetine (I-AA-MPD9):

- This double prodrug was synthesized according to Scheme 17 with appropriate modifications. This double prodrug I-AA-MPD9 was obtained as a yellow gum. ¹H-NMR (300 MHz, CDCl₃): δ 2.05-2.20 (m, 2H), 2.40 (s, 3H), 2.44 (s, 3H), 2.50-2.90 (m, 12H), 3.30-3.80 (m, 4H), 4.10-4.50 (m, 4H), 5.20 (bs, 1H), 6.42 (s, 1H), 6.87 (d, 2H, J = 8.52 Hz), 7.04-7.36 (m, 9H), 7.42 (d, 2H, J = 8.67 Hz). MS (m/z): 828 [M+H]⁺.

Example 52

Synthesis of double prodrug of gabapentin (I-AA-MPD10):

- 30 This double prodrug was synthesized as described below:

Step 1: A solution of SL-I (3.0 g, 19.4 mmol) in DMF (5 mL) was added to a suspension of CDI (9.46 g, 5.83 mmol) in DMF (15 mL) and stirred at RT for 20 h. The mixture was concentrated and the residue purified by column chromatography. The bis-imidazole obtained was used as such in the next step.

- 5 Step 2: A solution of the bis-imidazole (1.0 g, 2.91 mmol) in acetonitrile (3 mL) was added to a dispersion of gabapentin (1.49 g, 8.75 mmol) in 1N NaHCO₃ (8 mL) and stirred at RT for 3 d. The mixture was diluted with water, acidified with 2N HCl and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 1.04 g (65%) of pure I-M-MPP10 was obtained. ¹H-NMR (300 MHz, CDCl₃): δ 1.20-1.47 (m, 20H), 2.33 (s, 4H), 2.96 (t, 4H, J = 5.48 Hz), 3.23 (d, 4H, J = 6.5 Hz), 4.31 (t, 4H, J = 6.0 Hz), 5.55 (t, 2H, J = 6.6 Hz). ESI-MS (m/z): 547 [M-H]⁺.
- 10

Example 53

Synthesis of dotibate prodrug of gabapentin ethyl ester (MA-MPDIOF):

- A mixture of I-A1-PD8 (2.0 & 5.26 g, 10.53 mmol) and Hunig's base (2.75 mL, 15.8 mmol) in DCM (5 mL) was added to a solution of diphosgene (1.27 mL, 10.53 mmol) in DCM (4 mL) at 0 °C and stirred for 30 min. The mixture was concentrated, dissolved in DCM (10 mL) and treated with a solution of gabapentin ethyl ester hydrochloride (1.56 g, 7.85 mmol) and Hunig's base (2.74 mL, 15.77 mmol) in DCM (10 mL). The mixture was stirred for 3 h. After usual aqueous work-up, the crude material was purified by preparative HPLC to afford 2.2 g (69 %) of I-AA-MPDIOF as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 6H, J = 6.0 Hz), 1.35-1.67 (m, 2B), 2.21 (s, 4H), 2.91 (t, 4H, J = 6.0 Hz), 3.18 (d, 4H, J = 6.0 Hz), 4.12 (q, 4H, J = 6.0 Hz), 4.29 (t, 4H, J = 6.0 Hz), 5.42 (bs, 2H). MS; ES+ m/z 605 [M+H]⁺, 627 [M+Na]⁺.
- 15
- 20

Example 54

- 25 Synthesis of mutual prodrug of gabapentin and gabapentin (I-AArMMWI):

- To a solution of I-A1-PB4 (4.5 g, 10.32 mmol) in acetonitrile (40 mL) at RT was added CDI (2.0 g, 12.38 mmol) and stored for 3 h. To this was added a solution of gabapentin (2.12 g, 12.38 mmol) in 10 mL of 1N NaHCO₃ solution and the mixture was stored at RT for 24 h. After usual aqueous work-up and chromatographic purification, 2.6 g (40 %) of I-AA-MPDU was obtained as an off white solid. ¹H-NMR (CD₃OD, 400 MHz): δ 1.48 (m, 10H), 2.28 (s, 2H), 2.99 (t, 2H, J = 6.0 Hz), 3.06 (t, 2H, J = 6.3 Hz), 3.22 (s, 2H),
- 30

4Jl (t, 2H, $J = 6,0$ Hz), 4.46 (t, 2H, $J = 6,3$ Hz), 7.39-7.49 (m, 2H), 7.69-7.71 (m, 1H).
MS: (ES⁺) m/z 633,1 (M+H)⁺; 655.1 (M+Na)⁺.

Example 55

Synthesis of mutual prodrug of gabapentin ethyl ester and lamotrigine (I-AA-MPD12):

- 5 To a suspension of lamotrigine (2,70 g, 10.55 mmol) and PMAP (1,28 g, 10.55 mmol) in toluene (40 mL) at 110 °C was added a solution of the imidazole of I-A1-PD4 (4.99 g, 10.55 mmol) THF (20 mL) and stirred overnight at 110 °C. The reaction mixture was purified by column chromatography to afford 0.85 g (12 %) of I-AA-MPD12 as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.24 (t, 2H, $J = 7,2$ Hz), 1.36-1.77 (m, 10H), 2.29 (s, 2H), 2.93-3.03 (m, 4H), 3.22 (d, 2H, $J = 6,6$ Hz), 4.41 (q, 2H, $J = 7,2$ Hz), 4.34 (t, 2H, $J = 6,6$ Hz), 4.47 (t, 2H, $J = 6,3$ Hz), 5.65 (t, 1H), 7.34-7.41 (m, 2H), 7.60-7.63 (w, 1H). MS: ES⁺ m/z 61 (M+H)⁺, 682 (M+Na)⁺.
- 10

Example 56

Synthesis of mutual prodrug of gabapentin ethyl ester and levetiracetam (I-AA-MPI13):

- 15 To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (25 mL) and DCM (5 mL) at RT was added thionyl chloride (895 mg, 7.05 mmol). The reaction mixture was refluxed for 5 h, after which it was cooled to RT and a solution of I-A1-PD β (2.67 g, 7.05 mmol) in DCE (20 mL) was added drop-wise. The resulting mixture was stirred at RT for 18 h. After usual aqueous work-up and chromatographic purification, 1.63 g (48%) of I-AA-MPI13 was obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, 3H, $J = 7,4$ Hz), 1.25 (t, 3H, $J = 7,1$ Hz), 1.34-1.52 (m, 10H), 1.82-2.11 (m, 4H), 2.28 (s, 2H), 2.40 (t, 2H, $J = 7,0$ Hz), 2.89-2.94 (m, 4H), 3.04-3.11 (m, 1H), 3.19 (d, 2H, $J = 6,6$ Hz), 3.66-3.75 (m, 1H), 4.07-4.16 (m, 3H), 4.27-4.35 (m, 4H), 5.45 (t, 1H, $J = 6,5$ Hz), 8.18 (bs, 1H). MS: (ES⁺) m/z 576.1 [M+H]⁺; 598.1 [M+Na]⁺. CBS m/z 574.2 [M-H]⁺.
- 20

Example 57

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPDH4):

TBis (methyl) prodrug was synthesized according to method outlined in Scheme 18. This mutual prodrug I-AA-MPDH4 was obtained as oil. MS (m/z): 592 [M+H]⁺.

Example 58

- 30 Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPDIS):

This mutual prodrug was synthesized according to the method outlined in Scheme 18. The mutual prodrug I-M-MPD15 was obtained as a yellow oil MS (m/z) 620 [M+H]⁺.
Example 59

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MW16):

- 5 To a suspension of valpromide (750 mg, 5.24 mmol) in PCE (15 mL) at 0-5 °C was added oxalyl chloride (0.5 mL, 6.29 mmol) and refluxed overnight. The reaction mixture was cooled to RT, treated with a solution of I-A1-PD8 (2.18 g, 5.76 mmol) in DCE (2 mL) and stirred at RT for 2 h. The reaction mixture was purified by column chromatography to afford 1.61 g (51%) of I-AA-MPD16 as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.09 Hz), 1.25 (t, 3H, J = 6.96 Hz), 1.31-1.69 (m, 18H), 2.29 (s, 3H), 2.89-2.99 (m, 4H, J = 3.20 Hz), 3.20 (d, 2H, J = 6.47 Hz), 4.13 (q, 2H, J = 6.71 Hz), 4.40 (t, 2H, J = 5.97 Hz), 5.54 (t, 1H), 8.29 (br s, 1H). MS; ES+ m/z 549 [M+H]⁺, 571 [M+Na]⁺.

Example 60

- 15 Synthesis of double prodrug of valproic acid (I-AA-MEDM):

To a suspension of valpromide (3.0 g, 20.95 mmol) in DCE (30 mL) at 0-5 °C was added oxalyl chloride (1 mL, 15.08 mmol) and refluxed overnight. The reaction mixture was cooled to RT, a solution of SIA (0.805 g, 5.24 mmol) in PCE (3 mL) was added and stirred overnight. After usual work-up and chromatographic purification, 1.97 g (43%) of I-AA-MPD22 were obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 12H, J = 7.18 Hz), 1.28-1.66 (m, 16H), 2.94-2.95 (m, 2H), 3.02 (t, 2H, J = 6.51 Hz), 4.42 (t, 4H, J = 6.47 Hz). MS; m/z 493.2 [M+H]⁺, 510.0 [M+K]⁺, 515.10 [M+Na]⁺.

Example 61

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-AA-MPP27):

- 25 Step 1: To a solution of I-A1-PD8 (4.0 g, 10.54 mmol) in THF (25 mL) was added CDI (2.22 g, 13.7 mmol) and stirred at RT for 90 min. To this was added t-butyl carbazate (1.39 g, 10.54 mmol) and DMAP (1.288 g, 10.54 mmol), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.0 g (91%) of the intermediate carbazate-hydrazide was obtained as a colorless gummy material. ¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.31-1.74 (m, 10H), 2.30 (s,

2H), 2.90-3.10 (m, 4H), 3.20 (d, 2H, $J = 6.6$ Hz), 4.17 (q, 2H, $J = 7.1$ Hz), 4.32 (t, 2H, $J = 6.5$ Hz), 4.39 (t, 2H, $J = 6.5$ Hz), 5.42 (br s, 1H), 6.04 (br s, 1H), 6.98 (br s, 1H).

Step 2: To a solution of the above hydroxy acid (4.0 g, 7.44 mmol) in DCM (20 mL) was added 50% TFA/DCM (10 mL) and stirred at RT for 1h. DCM was removed under vacuum, the resulting residue triturated with diethyl ether (2 x 20 mL) and dried to give a colorless oil, which was dissolved in THF (20 mL). To the above solution at 0-5 °C was added TEA (2.1 g, 14.88 mmol), valproic acid (1.18 g, 8.184 mmol), PCC (2.3 g, 11.16 mmol) and DMAP (0.909 g, 7.44 mmol) and the mixture was stirred overnight at RT. The mixture was filtered, concentrated and purified by silica chromatography to afford 2.59 g (51 %) of **I-AA-MPD27** as a colorless gummy material. ¹H NMR (CDCl₃, 300 MHz): δ 0.85 (t, 6H, $J = 7.2$ Hz), 1.3 (t, 6H, $J = 7.11$ Hz), 1.2-1.80 (m, 26H), 2.2-2.3 (m, 1H), 2.35 (s, 2H), 2.81-2.94 (m, 4H), 3.21 (d, 2H, $J = 6.6$ Hz), 3.65-3.68 (m, 1H), 4.19 (q, 2H, $J = 7.1$ Hz), 4.36 (t, 2H, $J = 6.51$ Hz), 4.39 (t, 2H, $J = 6.51$ Hz), 5.51 (t, 1H), 8.17 (s, 1H). MS: m/z 712 [M+Naf], 728 [M+K⁺], 68S [M-H]⁻.

Step 3: To a solution of valproic acid (0.37 g, 2.56 mmol) in THF (5 mL) was added CDI (0.5 g, 3.08 mmol) and stirred for 2h. This was treated with a solution of the above TFA salt, TEA (0.7 mL, 5.13 mmol) and DMAP (50 mg, 0.41 mmol) in THF (10 mL) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.7 g (71%) of **I-CG-MPDI** was obtained as a white solid. ¹H NMR

Synthesis of mutual prodrug of valproic acid and nicotinic acid (**I-CC-MPDI**):

Step 1: To a solution of nicotinic acid (3.16 g, 17.76 mmol) and H₂-2c (3 g, 11.84 mmol) in THF (50 mL) was added TEA (8.3 mL, 59.2 mmol) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 4.14 g (97%) of H₂-2c-nicotinate ester was obtained as a colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.43 (s, 9H), 2.82 (t, 2H, $J = 6.31$ Hz), 3.42-3.48 (t, 2H), 4.62 (t, 2H, $J = 6.59$ Hz), 7.29-7.33 (m, 1H), 8.30 (d, 1H, $J = 7.95$ Hz), 8.73 (dd, 1H, $J = 4.56, 1.12$ Hz), 9.23 (d, 1H, $J = 2.13$ Hz). MS: m/z 358 [M+H]⁺, 381 [M+Naf], 739 [2M+K⁺].

Step 2: To a solution of H₂-2c-nicotinate ester (0.92 g, 2.50 mmol) in DCM (5 mL) was added 50% TFA/DCM (5 mL) and stirred for 1h. Reaction mixture was concentrated and the residual TFA salt was used as such in Step 3.

Step 3: To a solution of valproic acid (0.37 g, 2.56 mmol) in THF (5 mL) was added CDI (0.5 g, 3.08 mmol) and stirred for 2h. This was treated with a solution of the above TFA salt, TEA (0.7 mL, 5.13 mmol) and DMAP (50 mg, 0.41 mmol) in THF (10 mL) and the mixture was stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.7 g (71%) of **I-CG-MPDI** was obtained as a white solid. ¹H NMR

(CDCl₃, 500 MHz): δ 0.88 (t, 6H, J = 7 Hz), 1.25-1.59 (m, 8H), 2.06-2.08 (m, 1H), 2.86 (t, 2H, J = 6 Hz), 3.05 (t, 2H, J = 7 Hz), 3.58-3.61 (q, 2H, J = 9.0 Hz), 4.63 (t, 2H, J ~ 6.5 Hz), 7.40-7.42 (m, 1H), 8.30 (dt, 1H, J = 8.0, 2.0 Hz), 8.79 (dd, 1H, J = 5.0, 2.0 Hz), 9.23 (d, 1H, J = 0.5 Hz). MS; m/z 385 [M+H]⁺, 407 [M+Naf], 423 [M+K].

5 Example 63

Synthesis of mutual prodrug of valproic acid and nicotinic acid (I-CC-3MPD2);

This mutual prodrug was synthesized as described in Example 62, with obvious modifications, 0.612 g (41%) of I-CC-MPD2 was obtained as a white solid. ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (t, 6H, J = 7.23 Hz), 1.24-1.62 (m, 8H), 2.34-2.42 (m, 1H), 2.92 (t, 2H, J = 6.83 Hz), 3.75-3.84 (q, 2H, J = 6.04 Hz), 4.37 (t, 2H, J = 6.79 Hz), 7.36-7.41 (m, 1H), 8.15 (d, 1H, J = 7.92 Hz), 8.73 (d, 1H, J = 4.78 Hz), 9.02 (s, 1H). MS; m/z 385 [M+H]⁺, 419 [M+HCl], 383 [M-H].

Example 64

Synthesis of mutual prodrug of zidovudine and lamivudine (I-ffl-3MM):

15 Step 1; Synthesis of intermediate I-S17-PDX1:

4-Nitrophenyl chloroformate (0.27 g, 1.34 mmol) was added to a solution of the I-HI-P-5 (0.4 g, 0.89 mmol) and pyridine (76 μ l) in DCM (10 mL) and stirred at RT for 15 h. The mixture was concentrated and the residue purified by column chromatography to give 0.29 g (53%) of I-S17-PDW. ¹H-NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H), 2.45 (m, 2H), 2.97-3.06 (m, 4H), 4.05 (m, 1H), 4.41 (m, 1H), 4.40-4.49 (m, 4H), 4.54 (t, 2H, J = 6.5 Hz), 6.17 (t, 1H, J = 6.0 Hz), 7.33 (s, 1H), 7.39 (d, 2H, J = 4.8 Hz), 8.28 (d, 2H, J = 4.8 Hz) and 8.50 (s, 1H). MS (m/z): 635 [M+Naf].

Step 2: Synthesis of I-HH-MPD1; lamivudine (45 mg, 0.196 mmol) and DMAP (48 mg, 0.39 mmol) were added to a solution of I-S17-PDW (50 mg, 0.13 mmol) in PMF (1.5 mL) and stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography to give 40 mg (43%) of product I-HH-MPD1. ¹H-NMR (300 MHz, CDCl₃): δ 1.90 (s, 3H), 2.45 (t, 2H, J = 6.1 Hz), 3.05 (t, 4H, J ~ 6.2 Hz), 3.20 (m, 1H), 3.53 (m, 1H), 4.08 (m, 1H), 4.30-4.80 (m, 8H), 5.45 (t, 1H, J = 3.0 Hz), 5.90 (d, 1H, J = 7.5 Hz), 6.17 (t, 1H), 6.30 (t, 1H), 7.55 (s, 1H) and 7.90 (d, 1H, J = 7.50 Hz). MS (m/z): 725 [M+Naf].

Example 65

Synthesis of mutual prodrug of zidovudine and lamivudine (I-HH-MPD2b);

This mutual prodrug was synthesized according to the method outlined in Scheme 18.

The mutual prodrug I-HH-MPIWb was obtained as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 1.97 (s, 3H), 2.42 (m, 2H), 2.90-2.94 (m, 16H), 3.06 (m, 1H), 3.40-3.44 (m, 8H), 3.50-3.56 (m, 1H), 3.71-3.73 (m, 1H), 4.95 (m, 1H), 4.27-4.30 (t, 4H), 4.37-4.49 (m, 4H), 5.32 (t, 1H, J = 5.1 Hz), 5.83 (d, 1H, J = 6.6 Hz), 6.07 (m, 1H), 6.33 (bs, 1H), 7.20-7.25 (m, 1H), 7.74 (m, 1H). MS (m/z): 954 (M+Naf).

Example 66

Synthesis of mutual prodrug of cetirizine and pseudoephedrine (I-KA-MPD1):

Step 1: Synthesis of intermediate I-S17-P1:

This intermediate was prepared by reacting I-CH^{*}D10 with p-nitrophenyl chloroformate by a procedure as described in Example 64. The desired intermediate I-S17-PDU was obtained as a gum, ¹H-NMR (300 MHz, CDCl₃): δ 2.49-2.71 (m, 10H), 2.95 (t, 2H, J = 6.6 Hz), 3.01 (t, 2H, J = 6.5 Hz), 3.73 (bs, 2H), 4.13 (s, 2H), 4.22 (s, 1H), 4.41 (t, 2H, J = 6.6 Hz), 4.53 (t, 2H, J = 6.6 Hz), 7.48-7.40 (m, 11H), 8.28 (d, 2H, J = 7.1 Hz).

Step 2: The mutual prodrug I-CA-MPD1 was synthesized by reacting intermediate I-S17-PDU with pseudoephedrine by a procedure similar to that described in Example 64, Step 2. The desired mutual prodrug I-CA-MPD1 was obtained as a colorless granular material. ¹H-NMR (300 MHz, CDCl₃): δ 0.994, 0.9 (d, 3H, J = 6.6 Hz), 2.45 (bs, 4H), 2.68 (bs, 6H), 2.90 (s, 3H), 2.91-2.94 (m, 4H), 3.71 (bs, 3H), 4.41 (s, 2H), 4.18 (s, 1H), 4.26-4.41 (m, 4H), 4.56 (m, 2H), 7.17-7.35 (m, 11H). MS (m/z): 716 (M+H)⁺.

Example 67

Synthesis of mutual prodrug of gabapentin ethyl ester and naproxen (I-CA-MPD5):

The mutual prodrug was synthesized by reacting I-AI-PD8 and Naproxen according to Scheme 11, Method B. This mutual prodrug was obtained as colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, J = 7.1 Hz), 1.30-1.55 (m, 10H), 1.57 (t, 3H, J = 7.1 Hz), 2.27 (s, 2H), 2.54 (t, 4H, J = 6.4 Hz), 3.18 (d, 2H, J = 6.7 Hz), 3.80-3.88 (m, 1H), 3.91 (s, 3H), 4.12 (q, 2H, J = 7.1 Hz), 4.20-4.40 (m, 4H), 5.35 (s, 1H), 7.05-7.20 (m, 2H), 7.39 (dd, 1H, J = 1.8 Hz, 5.4 Hz), 7.60-7.73 (m, 3H). MS (m/z): 592 (M+H)⁺, 614 (M+Naf).

Example 68

Synthesis of mutual prodrug of valproic acid and nicotinic acid (**I-CA-MPD14**):

This mutual prodrug was synthesized using valproate and nicotmyl chloride hydrochloride, according to the methods described in Scheme 13 and Scheme 17, with obvious modifications. 1.0 g of the mutual prodrug **I-CA-MPDW** was obtained as a yellow oil. ^1H NMR (CD_3OD , 300 MBz): δ 0.87 (t, 6H, $J = 6$ Hz), 1.26-1.75 (m, 9H), 2.83 (s, 1H), 2.95-3.0 (m, 4H), 3.81 (t, 2H, $J = 6$ Hz), 4.44 (t, 2H, $J = 6$ Hz), 7.0 (s, 1H), 7.4 (bs, 1H), 7.42 (ra, 1H), 8.20 (d, 1H), 8.6S-8.74 (bs, 2H), ϵ 0 (s, 1H). MS: ES^+ m/z 428.1 $[\text{M}+\text{H}]^+$, 450.1 $[\text{M}+\text{Na}]^+$.

10 Example 69

Synthesis of mutual prodrug of valproic acid and nicotinic acid (**I-CA-MPDX5**):

To a solution of **I-C1-PD13** (1.5 g, 4.63 mmol) and nicotiny chloride hydrochloride (0.99 g, 5.56 mmol) in THF (25 mL) was added TEA (2 mL, 13.89 mmol) at 0 °C and stirred for 20 h at RT. After usual aqueous work-up and chromatographic purification, 1.0 g (83%) of **I-CA-MPDX5** was obtained as a yellow viscous liquid. ^1H NMR (CD_3OD , 500 MHz): δ 0.89 (t, 6H, $J = 5.0$ Hz), 1.29-1.73 (m, 9H), 1.64 (bs, 2H), 3 (t, 2H, $J = 5.0$ Hz), 3.07 (t, 2H, $J = 5.0$ Hz), 4.42 (t, 2H, $J = 5.0$ Hz), 4.63 (t, 2H, $J = 5.0$ Hz), 7.41-7.43 (m, 1H), 8.31 (bs, 1H), 8.78 (bs, 1H), 9.26 (s, 1H). MS: ES^+ m/z 429 $[\text{M}+\text{H}]^+$, 451 $[\text{M}+\text{Na}]^+$, 467 $[\text{M}+\text{K}]^+$.

20 Example 70

Synthesis of mutual prodrug of gabapentinyl ester and nicotinic acid (**I-CA-MWH8**):

To a solution of BOC deprotected **I-S12-PD2** (synthesized as described in Scheme 1, Method C and then deprotected using a known general deprotection method) (3.76 g, 7.64 mmol) in THF (30 mL) was added nicotiny chloride hydrochloride (1.5 g, 8.40 mmol), followed by TEA (4.26 mL, 30.56 mmol) and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 0.97 g (23 %) of **I-CA-MPD18** was obtained as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.24 (t, 3H, $J = 6.0$ Hz), 1.47 (m, 10H), 2.27 (s, 2H), 2.90-3.17 (m, 4H), 3.16 (d, 2H, $J = 6.0$ Hz), 3.79 (q, 2H, $J = 6.0$ Hz), 4.10 (q, 2H, $J = 6.0$ Hz), 4.36 (t, 2H, $J = 6.0$ Hz), 5.56 (bt, 1H, $J = 6.0$ Hz), 7.32-7.38 (m, 1H), 8.17 (d, 1H, $J = 9.0$ Hz), 8.71 (d, 1H, $J = 6.0$ Hz), 9.07 (s, 1H). MS: $(\text{ES})^+$ m/z 484 $(\text{M}+\text{H})^+$, 506 $(\text{M}+\text{Na})^+$; $(\text{ES})^-$ m/z 482 $(\text{M}-\text{H})^+$.

Example 71

Synthesis of mutual prodrug of levetiracetam and valproic acid (T-CA-MPD19);

To a solution of levetiracetam (1.0 g, 5.87 mmol) in DCE (20 mL) and PCM (4 mL) was added oxalyl chloride (894 mg, 7.05 mmol) and heated at 80 °C for 1 h. The reaction mixture was cooled to RT, a solution of I-C1-PP11 (1.97 g, 7.05 mmol) in DCE (10 mL) was added and stirred at RT for 18 h. After usual aqueous workup and chromatographic purification, 1.73 g (61 %) of X-CA-MPD19 was obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.85-0.91 (m, 9H), 1.24-1.62 (m, 5H), 1.80-2.05 (m, 4H), 2.34-2.44 (m, 3H), 2.91 (t, 4H, J = 6.0 Hz), 3.03-3.12 (m, 1H), 4.05-4.09 (m, 1H), 4.31-4.36 (m, 4H), 8.32 (bs, 1H). MS; (ES⁺) m/z 477.1 [M+H]⁺, 495.9 [M+Naf]⁺ (ES⁺) m/z 475.0 [M-H]⁻.

Example 72

Synthesis of mutual prodrug of gabapentin ethyl ester and valproic acid (I-CA-MPD21):

This mutual prodrug was synthesized by following a route depicted in Scheme 19, with obvious modifications. The mutual prodrug I-CA-MPD21 was obtained as a colorless oil. ¹H-NMR (CDCl₃, 300 MHz): δ 0.81 (t, 6H, J = 7.0 Hz), 1.60 (in, 21H), 2.20 (s, 2H), 2.25-2.35 (m, 1H), 2.84 (t, 4H, J = 6.6 Hz), 3.11 (d, 2H, J = 6.7 Hz), 4.05 (q, 2H, J = 7.0 Hz and 17.3 Hz), 4.15-4.25 (m, 4H), 5.43 (bt, 1H). MS (m/z): 506 [M+H]⁺, 528 [M+Naf]⁺.

Example 73

Synthesis of mutual prodrug of gabapentin ethyl ester and nicotinic acid (I-CA-MFD22):

To a suspension of nicotinic chloride hydrochloride (0.35 g, 1.97 mmol) in THF (3 mL) at 0 °C was added TEA (0.82 mL, 5.91 mmol). After 5 min, a solution of I-A1-PD8 (0.5 g, 1.97 mmol) and TEA (0.27 mL, 1.97 mmol) in THF (4 mL) was added and stirred overnight at RT. The mixture was purified by column chromatography to afford 0.573 g (90 %) of X-CA-MPD22 as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.24 (t, 3H, J = 6.0 Hz), 1.27-1.47 (m, 10H), 2.27 (s, 2H), 2.94 (t, 2H, J = 6.0 Hz), 3.07 (t, 2H, J = 6.0 Hz), 3.19 (d, 2H, J = 6.0 Hz), 4.12 (q, 2H, J = 6.0 Hz), 4.32 (t, 2H, J = 6.0 Hz), 4.62 (t, 2H, J = 6.0 Hz), 5.29 (bs, 1H), 7.36-7.42 (m, 1H), 8.30 (f, 1H, J = 3.0 Hz), 8.78 (dd, 1H, J = 1.69 Hz), 9.24 (s, 1H). MS: (ES⁺) m/z 455 (M+H)⁺, 507 (M+Naf)⁺.

Example 74

Synthesis of mutual prodrug of lamotrigine and valproic acid (I-CA-MPD23):

To a suspension of lamotrigine (0.455 g, 1.78 mmol) and OMAP (0.217 g, 1.78 mmol) in toluene (10 mL) at 110 °C was added a solution of the hydrazide of I-Cl-PPH (0.665 g, 1.78 mmol) in THF (5 mL). The reaction was stirred at 110 °C overnight and purified by column chromatography to afford 0.20 g (20%) of I-CA-MPD23 as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 0.86-0.90 (m, 6H), 1.20-1.62 (m, 6H), 1.53-1.62 (m, 2H), 2.36-2.39 (m, 1H), 2.90-3.0 (m, 4H), 4.34 (t, 2H, J = 6.3 Hz), 4.46 (t, 2H, J = 6.3 Hz), 7.36-7.38 (m, 2H), 7.60-7.63 (m, 1H). MS: (ES +) m/z 562 (M+H)⁺, 585 (M+Na)⁺.

10 Example 75

Synthesis of mutual prodrug of lamotrigine and nicotinic acid (I-CA-MPD24):

A solution of X-AX-FJM (0.5 g, 1.14 mmol) and TEA (0.5 mL, 2.87 mmol) in THF (5 mL) was added to a suspension of nicotinic anhydride (0.305 g, 1.71 mmol) and 0.5 mL TEA in THF (5 mL). The mixture was stirred at RT for 24 h. After usual aqueous workup and chromatographic purification, 0.15 g (14%) of I-CA-MPD24 were obtained as a white solid. ¹H NMR (CDCl₃, 500 MHz): δ 3.06 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.5 Hz), 4.49 (t, 2H, J = 6.5 Hz), 4.65 (t, 2H, J = 6.5 Hz), 7.38-7.43 (m, 3H), 7.60-7.62 (m, 1H), 8.33-8.36 (m, 1H), 8.81 (m, 1H), 9.35 (broad s, 1H). MS: (ES +) m/z 540.9 (M+H)⁺.

Example 16

20 Synthesis of mutual prodrug of lamotrigine and nicotinic acid (I-CA-MPD25):

This compound was synthesized using lamotrigine and nicotinic chloride hydrazide according to the methods outlined in Scheme 16 and Scheme 17. 0.8 g (44%) of I-CA-MPD25 HCl were obtained as an off white solid. ¹H NMR (D₂O, 500 MHz): δ 2.93 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.0 Hz), 3.69 (t, 2H, J = 6.5 Hz), 4.49 (m, 2H), 7.37-7.43 (m, 3H), 7.69-7.71 (m, 1H), 8.55-8.57 (m, 1H), 8.78-8.79 (m, 1H), 9.30 (broad s, 1H). MS: (ES +) m/z 539.9 (M+H)⁺, 561.8 (M+Na)⁺.

Example 77

Synthesis of mutual prodrug of metronidazole and norfloxacin (I-AH-MPD1):

Step 1: Synthesis of intermediate of I-HI-1:

30 CDI (319 mg, 1.97 mmol) was added to a solution of I-HX-PDI (577 mg, 1.64 mmol) in DMF (8 mL) and stirred at RT for 4 h. The mixture was concentrated and the residue

purified by column chromatography to give 395 mg (54%) of the imidazolidine of **I-HI-PBI**. ¹H-NMR (300 MHz, CDCl₃): δ 2.50 (s, 3H), 2.92 (t, 2H, J = 5.0 Hz), 3.00-3.10 (m, 2H), 4.36 (t, 2H, J = 3.0 Hz), 4.47-4.51 (m, 2H), 4.57-4.70 (m, 4H), 7.07 (s, 1H), 7.43 (s, 1H), 7.95 (s, 1H), 8.15 (s, 1H). MS (m/z): 446 [M+H]⁺.

- 5 Step 2: Synthesis of **I-AH-MPDI**: A solution of the imidazolidine of **I-HI-PDI** (100 mg, 0.224 mmol) in DMP (1 mL) was added to a suspension of norfloxacin (86 mg, 0.269 mmol) in DMF (2 mL) and stirred at RT for 60 h. The mixture was concentrated and the residue purified by column chromatography to give 35 mg (22%) of **I-AH-MPDI**. ¹H-NMR (300 MHz, CDCl₃): δ 1.59 (t, 3H, J = 7.5 Hz), 2.53 (s, 3H), 2.86-2.97 (m, 4H), 3.27-3.30 (m, 4H), 3.72 (t, 4H, J = 4.5 Hz), 4.32-4.40 (m, 4H), 4.48-4.52 (m, 2H), 4.59-4.63 (m, 2H), 6.85 (s, 1H, J = 6.0 Hz), 7.96 (s, 1H), 8.09 (d, 1H, J = 12.0 Hz), 8.68 (s, 1H). MS (m/z): 657 [M+H]⁺.
- 10

The following examples (Examples 78 - 80) were obtained according to procedure similar to those described, in Example 77, with the substitution of the

- 15 appropriate pairs of amino-containing and hydroxyl-containing therapeutic agents:

Example 78

Synthesis of mutual prodrug of metronidazole and norfloxacin (**I-AH-MPP3b**):

- The mutual prodrug **I-AH-MPP3b** was obtained as a yellow solid. ¹H-NMR (300 MHz, CDCl₃): δ 1.59 (t, 3H, J = 7.5 Hz), 2.49 (s, 3H), 2.82-2.95 (m, 10H), 3.30 (t, 4H, J = 4.5 Hz), 3.39 (bs, 4H), 3.72 (t, 4H, J = 4.8 Hz), 4.15 (dt, 8H, J = 26.2, 6.4 Hz), 4.61 (t, 2H, J = 4.8 Hz), 6.86 (d, 1H, J = 6.4 Hz), 7.75 (s, 1H), 8.07 (bd, 1H, J = 12.8 Hz), 8.67 (s, 1H), 14.9 (b, 1H). MS (m/z): 511.26 [M-H]⁺.
- 20

Example 79

Synthesis of mutual prodrug of gabapentin and tramadol (**I-AH-MPD7**):

- 25 The mutual prodrug was synthesized according to the method in Scheme 17 with obvious modifications. The mutual prodrug **I-AH-MPD7** was obtained as a colorless gummy material. ¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H, J = 7.1 Hz), 1.32-2.45 (m, 30H), 2.91-2.99 (m, 4H), 3.16 (t, 2H, J = 7.3 Hz), 3.80 (s, 3H), 4.08-4.15 (q, 2H, J = 7.1 Hz), 4.28-4.40 (m, 4H), 5.4 (s, 1H), 6.74-6.81 (m, 3H), 7.23-7.27 (t, 1H, J = 8 Hz). MS (m/z): 669.30 [M+H]⁺.
- 30

Example 80

Synthesis of mutual prodrug of venlafaxine and paroxetine (I-AH-MP8):

The mutual prodrug was synthesized according to the method outlined in Scheme 17 with obvious modifications. The mutual prodrug I-AH-MPD8 was obtained as a white sticky solid. ¹H-NMR was consistent with the expected structure. MS: m/z 812 [M]⁺.

5 Example 81

Synthesis of NO-releasing prodrug of Valproic acid (I-Cl-NOPDI):

The prodrug was synthesized as shown in Scheme W, Method B using as reagents valproic acid (725 mg, 5.03 mmol), Et₃N (1 g, 5.03 mmol), TEA (60 mg, 6.04 mmol), DCC (1.25 g, 6.04 mmol) and UMAP (10 mg). Yield: 532 mg (51%), ¹H-NMR (300 MHz, CDCl₃): δ 0.89 (t, 3H, J = 7.09 Hz), 1.22-1.77 (m, 8H), 2.36-2.40 (m, 1H), 2.93-3.00 (m, 4H), 4.34 (t, 2H, J = 6.8 Hz), 4.70 (t, 2H, J = 6.35 Hz). MS (CQ⁺ reagent): 326 [M+H]⁺.

Example 82

Synthesis of NO-releasing prodrug of valproic acid (I-O-NOPDI):

This prodrug was prepared as shown in Scheme 13, Method A. Thus, to a stirred mixture of valproyl isocyanate, which was freshly prepared from valproic acid (0.7 g, 4.90 mmol) [valproic acid was synthesized from valproic acid by using known methods as shown in Scheme 11, Method I) using a known method (*see J. Org. Chem.*, 1962, 27, 3742) in DCM (20 mL) at RT was added a solution of Et₃N (0.976 g, 4.90 mmol) in DCM (5 mL) drop-wise and stirred at RT for 2 h. The mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 0.6 g (33%) of prodrug I-Cl-NOPDI. ¹H-NMR data consistent with the expected structure. MS: [ES]⁺ m/z 391 [M+H]⁺, 407.2 [M+K]⁺; (Eq⁺ reagent) 368 [M+H]⁺.

Example 83

Synthesis of NO-releasing prodrug of aspirin (I-G1-NOPDI):

This prodrug was synthesized as shown in Scheme 11, Method D. Thus, to a solution of aspirin (3.0 g, 16.65 mmol) in THF (30 mL) at 0 °C was added oxalyl chloride (3.86 mL, 21.64 mmol) and heated at 70 °C for 2 h. The mixture was concentrated, the residue was dissolved in Et₃N (30 mL) and treated with a solution of LI-Ia (3.61 g, 16.65 mmol), TEA (3.48 mL, 24.97 mmol) and DMAP (361 mg) in THF (20 mL). The resulting mixture was stirred at RT for 2 h and filtered through celite. The filtrate was concentrated

and the residue purified by column chromatography to afford 3.06 g (48%) of the
 toamide SIMI, ¹H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 3.01-3.12 (m, 4H), 3.61 (t,
 2H, J = 6.5 Hz), 4.53 (t, 2H, J = 6.0 Hz), 7.11 (dd, 1H, J = 8 Hz, 1 Hz), 7.32 (t, 2H, J =
 7.6 Hz), 7.57 (t, 1H, J = 7.6 Hz), 8.03 (dd, 1H, J = 7.8 Hz, 1 Hz), MS (ES⁺) m/z: 403.92
 5 (MW-

To a solution of SII-II (2.0 g, 5.27 mmol) in acetonitrile (20 mL) at 0 °C was added
 AgNO₃ (1.07 g, 6.32 mmol) in the dark. The mixture was stirred at RT for 1.5 h, filtered
 through celite and concentrated. The residue, after usual aqueous work-up and
 chromatographic purification, afforded 0.965 g (50%) pure I-CtSFOHR. ¹H-NMR (300
 10 MHz, CDCl₃): δ 2.36 (s, 3H), 2.98 (t, 2H, J = 6.8 Hz), 3.05 (t, 2H, J = 6.4 Hz), 4.54 (t,
 2H, J = 6.4 Hz), 4.70 (t, 2H, J = 6.8 Hz), 7.12 (d, 1H, J = 8 Hz), 7.33 (t, 1H, J = 7.6 Hz),
 7.59 (t, 1H, J = 7.5 Hz), 8.03 (dd, 1H, J = 7.8 Hz, 1 Hz). MS (ES)⁺ m/z: 379, 11
 (M+NE)⁺, 383, 98 (M+Na)⁺,

Example 84

15 Synthesis of NO-releasing prodrug of aspirin (I-Cl-NOPHSa):

As shown in Scheme 11, Method H, this prodrug was synthesized in three steps:

Step 1: To a suspension of aspirin (1 g, 5.55 mmol) in benzene (15 mL) and DMF (1
 drop) at 0-5 °C was added a solution of oxalyl chloride (0.6 mL, 6.66 mmol) in benzene
 (5 mL) and stirred at 85 °C for 2 h. The reaction mixture was concentrated, and the crude
 20 acid chloride was used immediately in the next step.

Step 2; To a solution of the above acid chloride in benzene (30 mL) was added silver
 cyanate (998 mg, 6.66 mmol) and refluxed in the dark for 1 h. The mixture, containing 2-
 acetoxybenzoyl isocyanate, was cooled to RT and used in the next step.

Step 3: To the above mixture was added a solution of U-2b (1.33 g, 6.66 mmol) in
 25 benzene (5 mL) and stirred at RT for 1 h. The mixture was filtered through celite and
 concentrated, and the residue was purified by column chromatography to afford 1.2 g
 (54%) of pure I-Cl-NOOPHSa. ¹H-NMR data is consistent with the expected Structure.
 MS (ES⁺) m/z: 404.98 (TW-Hf), 426.94 [M+H]⁺, 442.97 [M+Rf]⁺, (BS⁺) m/z 403.01 (M-
 H)⁺.

30 Example 85

Synthesis of sodium salt of NO-releasing prodrug of aspirin, OI-Cl-NOHSb):

To a suspension of 60% sodium hydride (45 mg, 1.3 mmol) in THF (0.5 mL) was added solution of I-CI-NOPD5a (500 mg, 1.24 mmol) in THF (1.5 mL). After stirring for 5 min, THF was removed under vacuum, the residue was washed with dry Et₂O (4 x 3 mL) to remove unreacted starting material and dried in vacuum to afford 410 mg (78%) of I-CI-NOPX as an off-white solid, ¹H NMR (D₂O, 500 MHz): δ 2.28 (s, 3H), 2.93-2.97 (m, 4H), 4.33 (t, 2H, J = 6.0 Hz), 4.68 (t, 2H, J = 7.2 Hz), 7.07 (d, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 7.5 Hz), 7.41 (t, 1H, J = 9.0 Hz), 7.57 (d, 1H, J = 7.5 Hz). MS: m/z 427.0 (M+H)⁺, 449.0 (M+HNa)⁺.

Example #6

10 Synthesis of NO-releasing prodrug of aspirin (I-CI-NOHPM):

This prodrug was synthesized as shown in Scheme 11, Method E. Thus, to a solution of aspirin (1.20 g, 6.70 mmol) in DCM (15 mL) at 0 °C was added oxalyl chloride (0.74 mL, 8.65 mmol) and stirred at RT for 1.5 h. The mixture was concentrated and the residual acid chloride was treated with Et₃N-TFA (6.70 mmol) in DCM (14 mL), followed by drop-wise addition of TEA (3.73 mL, 26.81 mmol) at 0 °C. The mixture was stirred at RT for 4 h and concentrated. The residue, after usual aqueous work-up and chromatographic purification, gave 0.822 g (34 %) of I-CI-NOHPM. ¹H-NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H), 2.92 (t, 2H, J = 6.11 Hz), 2.98 (t, 2H, J = 6.0 Hz), 3.76 (q, 2H, J = 6.0 Hz), 4.71 (t, 2H, J = 6.0 Hz), 6.70 (bs, 1H), 7.10 (d, 1H, J = 9.0 Hz), 7.31-7.33 (m, 1H), 7.48-7.50 (m, 1H), 7.78 (d, 1H, J = 8.0 Hz). MS (EI)⁺ m/z: 361 (M+H)⁺.

Examples?

Synthesis of NO-releasing prodrug of nicotinic acid (I-CI-PJOPD7):

This prodrug was synthesized as shown in Scheme 11, Method C. Thus, to a suspension of nicotinyl chloride hydrochloride (2.68 g, 15.07 mmol) in THF (10 mL) at 0 °C was added a solution of 11-21 (2.0 g, 10.05 mmol) and TEA (5.6 mL, 40.2 mmol) in THF (7 mL) and stirred at RT for 15 h. The mixture was filtered, concentrated and the residue purified by column chromatography to afford 2.23 g (73%) of pure I-CH-NOFDT. ¹H-NMR (300 MHz, CDCl₃): δ 3.01 (t, 2H, J = 4.75 Hz), 3.09 (t, 2H, J = 6.5 Hz), 4.63 (t, 2H, J = 5.25 Hz), 4.70 (t, 2H, J = 4.75 Hz), 7.37 - 7.42 (m, 1H), 7.59-7.61 (d, 1H, J = 8 Hz, 2H), 8.78-8.80 (dd, 1H, J = 2 Hz), 9.23 (d, 1H, J = 2 Hz). MS (ES)⁺ m/z: 305 (M+H)⁺.

Example 88

Synthesis of NO-releasing prodrug of nicotinamide (MTI-NOPD β a):

This prodrug was synthesized from nicotinamide (1 g, 8.18 mmol) according to the procedure described in *Sample 77* (see Scheme 11, Method I or Scheme 13, Method A).

- 5 After usual workup, the crude product was purified by column chromatography to afford 0.1 g (3.5%) of prodrug K14røPD8ft. $^1\text{H-NMR}$ (300 MHz, CDCl_3) = β 2.97-3.0 (m, 4H), 4.51 (t, 2H, $J = 6.3$ Hz), 4.73 (t, 2H, $J = 6.7$ Hz), 7.38-7.48 (m, 1H), 8.16-8.22 (m, 1H), 8.71-8.79 (m, 2H), 9.04 (s, 1H). MS [ESI] m/z : 348 $[\text{M}+\text{H}]^+$, 370 $[\text{M}+\text{Naf}]^+$.

Examples?

- 10 Synthesis of NO-releasing prodrug of nicotinic acid (I-Cl-NOPJW):

This prodrug was synthesized as shown in Scheme 11, Method F. Thus, TEA (6.92 mL, 50.55 mmol) was added to a suspension of acetyl chloride hydrochloride (3.0 g, 16.85 mmol) and cysteamine hydrochloride (241 g, 18.53 mmol) in DCM (30 mL) at 0 °C and stirred at RT for 4 h. The mixture was concentrated and the residue dissolved in MeOH

- 15 (20 mL). To this solution at 0 °C was added a solution of LI-3b (4.11 g, 16.85 mmol) in MeOH (5 mL), followed by TEA (4.61 mL, 33.70 mmol) and stirred overnight at RT. The mixture was filtered through celite, concentrated and the residue was purified by column chromatography to afford 3 g (58%) of pure I-Cl-NOPD9. $^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$): 2.94 (t, 2H, $J = 6-7$ Hz), 3.09 (t, 2H, $J = 6.3$ Hz), 3.56 (q, 2H, $J = 6.3$ Hz), 20 4.73 (t, 2H, $J = 6.3$ Hz), 7.49-7.53 (m, 1H), 8.16-8.19 (m, 1H), 8.69-8.70 (m, 1H), 8.87 (bt, 1H), 8.98 (s, 1H). MS (ESI) m/z : 304 $[\text{M}+\text{H}]^+$, 326 $[\text{M}-\text{H}]^+$.

Example 90

Synthesis of NO-releasing prodrug of naproxen α (I-Cl-NOPDIO):

This prodrug was synthesized as shown in Scheme 11, Method B. Thus, to a solution of naproxen (2.23 g, 9.7 mmol) and M-2b (1.93 g, 9.7 mmol) in THF (70 mL) at RT were added DCC (3 g, 14.55 mmol) and PMAF (1.78 g, 14.55 mmol) and stored overnight.

- 25 The mixture was filtered and concentrated, and the residue purified by column chromatography to afford 1.03 g (25%) of pure I-Cl-NOPDIO. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.59 (d, 3H, $J = 7-16$ Hz), 2.81 (t, 2H, $J = 6.77$ Hz), 2.97 (q, 2H, $J = 6.42$ Hz), 3.85-3.88 (m, 1H), 3.91 (s, 3H), 4.33 (t, 2H, $J = 5.26$ Hz), 4.53 (t, 2H, $J = 6.79$ Hz), 7.10-7.16 (m, 2H), 7.41 (d, 1H, $J = 1.7$ Hz), 7.69 (d, 3H, $J = 5.55$ Hz).
- 30

Example 91

Synthesis of NO-releasing prodrug of naproxen (I-CI-NOP&to):

This prodrug was synthesized as shown in Scheme U, Method E. To a solution of
 5 naproxen (1.69 g, 7.37 mmol) in chloroform (20 mL) at 0-5 °C was added oxalyl
 chloride (0.8 mL, 8.84 mmol), followed by 2-3 drops of DMF. The mixture was stirred
 at RT for 90 min and concentrated. This acid chloride (~7.37 mmol) was treated with Li-
 5. TFA (6.7 mmol) in TBF (20 mL) and cooled to 0 °C. To this was added TEA (5.6 mL,
 40 mmol) and stirred at RT for 3 h. The mixture was concentrated and the residue, after
 10 usual aqueous work-up and chromatographic purification, afforded 0.409 g (14%) of pure
 (S)-α-(6-chloro-2-naphthyl)-2-naphthol. ¹H-NMR (CDCl₃, 300 MHz): δ 1.24 (d, 3H), 2.87 (t, 2H, J = 6.5 Hz),
 2.93 (t, 2H, J = 6.7 Hz), 3.64 (q, 2H, 7.5 Hz), 3.76 (m, 1H), 3.88 (s, 3H), 4.10 (t, 2H, J =
 6.6 Hz), 4.79 (br s, 1H), 6.97-7.08 (m, 3H), 7.35-7.46 (m, 3H).

Example 92

15 Synthesis of NO-releasing prodrug of flurbiprofen (I-CI-NOM>13):

This prodrug was synthesized as shown in Scheme U, Method A, using as reagents
 flurbiprofen (4.0 g, 16.37 mmol), CDI (3.97 g, 24.56 mmol) and Li-2b (325 g, 1637
 mmol). Yield; 3 g (43%). ¹H-NMR (300 MHz, CDCl₃): δ 1.56 (d, 3H, J = 11 Hz), 2.80-
 3.0 (m, 4H, J = 5.67 Hz), 3.78 (q, 1H, J = 7.10 Hz), 4.36 (m, 2H), 4.78 (t, 2H, J = 6.78),
 20 7.11-7.54 (m, 8H).

Example 93

Synthesis of NO-releasing prodrug of flurbiprofen (J-CI-NOPDWa):

This prodrug was synthesized as shown in Scheme 11, Method I. To a solution of
 flurbiprofen (5.0 g, 20.46 mmol) in benzene (50 mL) was added oxalyl chloride (3.11 g,
 25 24.55 mmol) at 0 °C and 2 drops of DMF and stirred at RT for 20 min. Benzene was
 removed under vacuum and the residue was diluted with DCM (50 mL). The reaction
 mixture was cooled to 0 °C and dry ammonia was passed for 30 min. The reaction
 mixture was concentrated and, after usual aqueous work-up, 4.5 g of flurbiprofen amide
 was obtained as a white solid.

30 To a solution of flurbiprofen amide (3.0 g, 12.33 mmol) in DCM (70 mL) was
 added oxalyl chloride (1.87 g, 14.79 mmol) at 0 °C and refluxed for 16 h. The reaction mixture

was cooled to RT and treated with Li-2⁺ (2.45 g, 12.33 mmol) in DCE (10 mL) and stirred overnight. After usual aqueous work-up and chromatographic purification, 0.5 g of PCI-NOJPJ¹Ma were obtained. ¹H NMR (CDCl₃, 300 MHz): 5.155 (d, 3H, $J = 6.9$ Hz), 2.94-2.97 (bs, 4H), 4.38-4.47 (bs, 3H), 4.68 (t, 2H, $J = 6.6$ Hz), 7.13-7.55 (bs, 8H). MS: ES⁺ m/z 469.03 [M+H]⁺, 467.16 [M-H]⁺.

Example 94

Synthesis of NO-releasing prodrug of flurbiprofen (I-Cl-NOPDISb):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of flurbiprofen (2.5 g, 10.23 mmol) in THF (30 mL) was added CDI (3.31 g, 20.46 mmol) and stirred at RT for 16 h. To this was added I-S.TFA (3.64 g, 10.23 mmol) in THF (15 mL), followed by TEA (2.85 mL, 20.46 mmol) and stirred for 16 h. After usual work-up and chromatographic purification, 1.5 g (91%) of I-Cl-NOPDISb were obtained. ¹H NMR (CDCl₃, 300 MHz): 8.15 (d, 3H, $J = 6.9$ Hz), 2.82 (t, 2H, $J = 6.3$ Hz), 2.92 (t, 2H, $J = 6.9$ Hz), 3.50 (m, 3H), 4.6 (t, 2H, $J = 6.6$ Hz), 5.8 (s, 1H), 7.1-7.55 (bs, 8H). MS: ES⁺ m/z 425.21 [M+H]⁺, 423.11 [M-H]⁺.

Example 95

Synthesis of NO-releasing prodrug of indomethacin (I-Cl-NOPIM6):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of indomethacin (2.0 & 5.59 mmol) in chloroform (25 mL) was added CDI (1.09 g, 6.71 mmol) and stirred for 2 h. A solution of U-2b (1.22 g, 6.15 mmol) and DMAP (751 mg, 6.15 mmol) in chloroform (5 mL) was added, and the mixture was stirred at RT for 16 h. After usual aqueous work-up and chromatographic purification, 2.02 g (67%) of pure I-CX-NOme was obtained. ¹H-NMR (300 MHz, CDCl₃): 8.239 (s, 3H), 2.88-2.95 (m, 4H), 3.69 (s, 2H), 3.7 (s, 3H), 4.38 (t, 2H, $J = 6.3$ Hz), 4.63 (t, 2H, $J = 6.6$ Hz), 6.67 (dd, 1H, $J = 2.4, 8.7$ Hz), 6.87 (d, 1H, $J = 8.7$ Hz), 6.96 (d, 1H, $J = 2.4$ Hz), 7.47 (d, 2H, $J = 8.4$ Hz), 7.67 (d, 2H, $J = 8.4$ Hz). MS (ES⁺) m/z : 539.2 [M+H]⁺, 560.79 [M+Na]⁺.

Example 96

Synthesis of NO-releasing prodrug of indomethacin (I-Cl-NOPP18):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of indomethacin (3.01 g, 8.42 mmol) in THF (50 mL) at RT was added CDI (1.64 g, 10.1 mmol). After 1 h, I-S.TFA (3 g, 8.42 mmol) was added at 0 °C, followed by TEA (5.9

mL, 42.1 mmol) and DMAP (0.6 g, 4.91 mmol). The reaction mixture was stirred at RT for 2 d. After usual aqueous work-up and chromatographic purification, 3.16 g (70%) of **1-Cl-NOPDIS** were obtained as yellow solid. ¹H NMR (CDCl₃, 300 MHz): δ 2.38 (s, 3H), 2.79 (t, 2H, J = 6.3 Hz), 2.56 (m, J < 6.9 Hz), 3.54 (q, 2H, J < 6.0 Hz), 3.66 (t, 2H, J = 6.1 Hz), 3.83 (s, 3H), 4.61 (t, 2H, J < 6.6 Hz), 6.01 (bs, 1H), 6.71 (d, 1H, J < 2.1, 9.0 Hz), 6.9 (dd, 2H, J = 3.3, 8.1 Hz), 7.49 (d, 2H, J = 8.4 Hz, 2H), 7.66 (d, 2H, J = 8.4 Hz). MS: m/z 538.10 [M+H]⁺, 560.1 [M+Na]⁺.

Example 97

Synthesis of NO-releasing prodrug of ketoprofen (**1-Cl-NOPDIS**):

This prodrug was synthesized as shown in Scheme 11, Method A according to the method described in Example 96 using as reagents ketoprofen (1.27 g, 5 mmol), CDI (1.21 g, 7.5 mmol) and DIPEA (1.2 g, 5 mmol). Yield: 0.6 g (51%). ¹H-NMR (300 MHz, CDCl₃): δ 1.55 (d, 3H, J < 7.0 Hz), 2.80-2.95 (m, 4H), 3.82 (q, 1H, J = 6.7 Hz), 4.35 (t, 2H, J = 6.1 Hz), 4.64 (t, 2H, J = 6.5 Hz), 7.40-7.85 (m, 9H). MS (ES⁺) m/z: 436.06 [M+H]⁺, 458.02 [M+Na]⁺.

Example 98

Synthesis of NO-releasing prodrug of ketoprofen (**1-Cl-NOPD20a**):

This prodrug was synthesized as shown in Scheme 11, Method A. Thus, to a solution of the amide of ketoprofen (1.78 g, 7 mmol) in PCE (70 mL) was added **W-2B** (1.0 g, 8.4 mmol) at 0 °C and stirred for 16 h. After cooling to RT, a solution of **W-2B** (1.4 g, 7 mmol) in PCE (10 mL) was added and stirred for 20 h. After usual aqueous work-up and chromatographic purification, 0.6 g (17 %) of **1-Cl-NOPD20a** was obtained as a pale yellow gum. ¹H NMR (CDCl₃, 300 MHz): δ 1.47 (d, 3H, J = 6.96 Hz), 3.00 (bs, 4H), 4.00 (q, 1H, J = 6.51 Hz), 4.39 (t, 2H, J = 6.21 Hz), 4.68 (bs, 2H), 7.47-7.77 (bs, 9H). MS: ES⁺ m/z 478 [M+H]⁺, 477.1 [M+Na]⁺.

Example 99

Synthesis of NO-releasing prodrug of diclofenac (**1-Cl-NOPD22**):

This prodrug was synthesized as shown in Scheme 11, Method B, using as reagents diclofenac (1.0 g, 3.378 mmol), **W-2B** (0.68 g, 3.37 mmol), DMF (5 mL), DCC (0.835 g, 4.054 mmol) and PMAP (0.082 g, 0.675 mmol). Yield: 0.35 g (24 %). ¹H-NMR (300 MHz, CDCl₃): δ 2.91-3.04 (m, 4H), 3.85 (s, 2H), 4.42 (t, 2H, J = 6.6 Hz), 4.72 (t, 2H, J =

6.6 Hz), 6.56 (d, 1H, J = 8.1 Hz), 6.82 (g, 1H), 6.94-7.03 (m, 2H), 7.12-7.27 (m, 1H), 7.35 (d, 1H, J = 8.1 Hz). MS (ES⁺) m/z: 476.90 (M+H⁺), 498.86 (M+Na⁺).

Example 100

Synthesis of NO-releasing prodrug of flurbiprofen (I-C1-NOPD26):

S The prodrug was synthesized as outlined in Scheme 20. Thus, to a solution of 20-11 (0.8 g, 2.90 mmol) in THF (10 mL) and DMF (10 mL) was added the cesium salt of flurbiprofen (1.2 g, 3.19 mmol) and stirred at RT for 2 h. After usual aqueous work-up and chromatographic purification, 1.13 g (80 %) of I-C1-NOPD26 was obtained as a light yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 1.58 (s, 3H, J = 7.5 Hz), 2.88-2.94 (m, 4H), 3.88 (q, 1H, J = 7.0 Hz), 4.40 (t, 2H, J = 6.5 Hz), 4.64-4.68 (m, 4H), 7.14-7.54 (m, 5H). MS: m/z [M+H]⁺, 506.1 [M+Na]⁺.

Example 101

Synthesis of NO-releasing prodrug of gabapentin ethyl ester (I-A1-NOPD1);

This prodrug was synthesized as shown in Scheme 12, Method A. Thus, to a stirred solution of diphosgene (0.88 mL, 7.37 mmol) in DCM (3 mL) at 0 °C was added dropwise a solution of LI-2a (0.80 g, 3.68 mmol) and Hunig's base (1.92 mL, 11.85 mmol) in DCM (1 mL). The mixture was stirred at 0 °C for 30 min, and concentrated. The residue was dissolved in DCM (4 mL) and treated with gabapentin ethyl ester hydrochloride (0.95 g, 4.05 mmol) & Hunig's base (1.39 mL, 8.05 mmol). The mixture was stirred at RT for 3 h and concentrated. The residue, after usual aqueous work-up, gave 1.6 g (98 %) of I-A1-NOPD1. ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 444 [M+H]⁺, 465.9 [M+Na]⁺.

To a stirred solution of I-S12-IX (1.3 g, 2.94 mmol) in acetonitrile (5 mL) at RT was added silver nitrate (0.6 & 3.52 mmol) portion-wise and stirred at RT for 2.5 h. After filtration through celite, the filtrate was concentrated and the residue purified by column chromatography to afford 0.561 g (45 %) of prodrug I-A1-NOPD1. ¹H-NMR data is consistent with the expected structure. MS (ES⁺) m/z: 425 (M+H)⁺, 447 (M+Na)⁺.

Example X02

Synthesis of NO-releasing prodrug of lamotrigine (I-A1-NOPD3a and X-A1-NOPD3b):

30 This prodrug was synthesized as shown in Scheme 12, Method B. Thus, to a suspension of lamotrigine (1 g, 3.90 mmol) in toluene (20 mL) at 120 °C was added dropwise a

solution of the imidazolidine of *LbIb* (1.4 g, 4.70 mmol) in THF (10 mL) and refluxed for 6 h. After usual aqueous work-up and chromatographic purification, 340 mg (20%) of I-AI-NOPD-3a/b was obtained. ¹H-NMR data is consistent with the expected structure. MS (ES)⁺ m/z: 481 (M+H)⁺.

5 Example 103

Synthesis of NO-releasing prodrug of nicotinic hydrazide (I-AI-NOPD4):

The prodrug was synthesized from nicotinic hydrate (235 mg, 1.70 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.21 g (34%) of prodrug I-AI-NOPD4. ¹H-NMR (300 MHz, DMSO-d₆): δ 3.02 (t, 2H, J = 5.8 Hz), 3.10 (v 2H, J = 6.1 Hz), 4.28 (t, 2H, J = 5.8 Hz), 4.76 (t, 2H, J = 6.1 Hz), 7.5J-7.55 (dd, 1H, J = 4.8 Hz, 7.7 Hz), 8.17 (d, 1H, J = 7.1 Hz), 8.74 (d, 1H, J = 3.8 Hz), 8.88 (s, 1H), 9.44 (bs, 1H), 10.54 (fas, 1H). MS (ESI)⁺ m/z: 363 [M+H]⁺.

Example 104

15 Synthesis of NO-releasing prodrug of Lisinopril dimethyl ester (I-AI-NOPDS):

This prodrug was synthesized from Lisinopril dimethyl ester hydrochloride (1.10 g, 2.56 mmol) according to the procedure described in Example 101 (see Scheme 12, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.76 g (67%) of prodrug I-AI-NOPDS. ¹H-NMR (300 MHz, CDCl₃): δ 1.49-1.54 (m, 2H), 1.93-2.07 (m, 2H), 2.12-2.25 (m, 1H), 2.64-2.68 (m, 2H), 2.91-3.0 (m, 4H), 3.18-3.25 (m, 3H), 3.42-3.47 (m, 1H), 3.52-3.55 (m, 2H), 3.69 (s, 3H), 3.73 (s, 3H), 4.28 (t, J = 6.3 Hz, 2H), 4.47-5.05 (m, 1H), 4.69 (t, J = 6.8 Hz, 2H), 5.22 (bt, 1H), 7.14-7.19 (m, 3H), 7.23-7.28 (m, 2H). MS (ESI)⁺ m/z: 659 (M+H)⁺.

Example 105

25 Synthesis of NO-releasing prodrug of omeprazole (I-AI-NOPM):

This prodrug was synthesized as shown in Scheme 12, Method B. To an ice-cold solution of diphosgene (0.3 mL, 2.48 mmol) in toluene at 0 °C, was added a mixture of *U-Ob* (0.5 g, 2.51 mmol) and TCA (0.42 mL, 3.0 mmol) in toluene (3 mL) and stirred for 2 h. In a separate flask, omeprazole (0.867 g, 2.50 mmol) was dissolved in THF (5 mL), cooled to 0 °C and NaH (0.059 g, 2.5 mmol) was added. The mixture was stirred for 30 min, the above reaction mixture was added dropwise to it and stirred for 2 h. After usual aqueous

work-up and chromatographic purification, 0.23 g (20 %) of I-A1-NOPD6 was obtained as a reddish-yellow gum. MS: ES+ m/z 571 ($M+H$)⁺, 593 ($M+Na$)⁺.

Example 106

Synthesis of NO-releasing prodrug of hydralazine (I-A1-NOPDT):

- 5 This prodrug was synthesized from hydralazine hydrochloride (0.99g, 5.01 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 0.8 g (41%) of prodrug I-A1-NOPDT. ¹H-NMR (300 MHz, CDCl₃): δ 2.95-3.06 (m, 4H), 4.43 (t, 2H, J = 6.35 Hz), 4.69 (t, 2H, J = 6.7 Hz), 7.57 (m, 1H), 7.63-7.71 (m, 2H), 8.16 (s, 1H), 8.29 (d, 1H, J = 7.6 Hz). MS (ES⁺) m/z : 386.05 ($M+H$)⁺.
- 10

Example 107

Synthesis of NO-releasing prodrug of amlodipine (I-A1-NOED8):

- Thus prodrug was synthesized from amlodipine (1.67 g, 4.09 mmol) according to the procedure described in Example 109 (see Scheme 12, Method B). After usual workup,
- 15 the crude product was purified by column chromatography to afford 1.33 g (61%) of I-A1-NOED8. ¹H-NMR (300 MHz, CDCl₃): δ 1.18 (t, 3H, J = 7.1 Hz), 2.36 (s, 3H), 2.93-2.99 (m, 4H), 3.47 (bs, 2H), 3.61-3.64 (m, 5H), 4.04 (q, 2H, J = 7.1 Hz), 4.35 (w, 2H), 4.68-4.74 (m, 4H), 5.0 (br, 1H), 7.13-7.36 (m, 4H). MS (ES⁺) m/z : 634.14 ($M+H$)⁺, 656.83 ($M+Na$)⁺; (BS⁺) m/z : 634.94 ($M+H$)⁺.

- 20 Example 108

Synthesis of NO-releasing prodrug of levetiracetam (I-A2-NOFTOa):

- The prodrug was synthesized from levetiracetam (1.0 g, 5.87 mmol) according to the procedure generally described in Example 82 (see Scheme 13, Method A). After usual workup and chromatographic purification, the product was further purified by preparative
- 25 HPLC to afford 728 mg (31%) of prodrug I-A2-NOFTOa. ¹H-NMR was consistent with the expected structure. MS (BS⁺) m/z : 396.1 [$M+H$]⁺, 418.1 [$M+Na$]⁺, (ES⁺) m/z : 394.1 [$M+H$]⁺.

Example 109

Synthesis of NO-releasing prodrug of valdecoxib (I-A3-KOPD Ja):

- 30

This prodrug was synthesized as shown in Scheme 13, Method B. Thus, to a cold suspension of sodium hydride (271 mg, 6.81 mmol) in THF (7 mL) was added dropwise a solution of valdecoxib (1.8 g, 5.68 mmol) in THF (15 mL) and stirred at RT for 2 h. A solution of the hydrazide of **U-2b** (2.0 g, 6.81 mmol) in THF (15 mL) was added and stirred at room temperature for 1 h. The reaction mixture was concentrated and the residue, after usual aqueous work-up and chromatographic purification, afforded 976 mg (32 %) of prodrug **I-A3-NOPDIa**. ¹H-NMR data is consistent with the expected structure. MS (ES)⁺ *m/z*: 538 [M-H]⁺.

Example 10

10 Synthesis of NO-releasing prodrug of celecoxib (**I-A3-NOPDIa**):

This prodrug was synthesized from celecoxib (6.62 g, 17.35 mmol) according to the procedure described in Example 109 (see Scheme 13, Method B). After usual workup, the crude product was purified by column chromatography to afford 1.55 g (15%) of prodrug **I-A3-NOPDIa**. ¹H-NMR (300 MHz, CDCl₃): 5.238 (s, 3H), 184-2.98 (m, 4H), 4.34 (t, 2H, J = 6.45 Hz), 4.63-4.71 (m, 2H), 6.74 (s, 1H), 7.09-7.25 (m, 4H), 7.51 (d, 2H, J = 6.8 Hz), 8.02 (d, 2H, J = 6.8 Hz). MS (ES)⁺ *m/z*: 606.87 [M + H]⁺, 628.73 [M + Na]⁺; (ES)⁺ *m/z*: 604.58 [M-H]⁺.

Example 11

Synthesis of NO-releasing prodrug of paracetamol (**I-HX-NOPDI**):

This prodrug was synthesized as shown in Scheme 14, Method B. Thus, to a solution of paracetamol (2.0 g, 13.24 mmol) in THF (20 mL) was added CDI (2.36 g, 14.57 mmol) and the mixture was stirred at RT for 3 h. To this was added a solution of **LI-2b** (1.21 g, 6.62 mmol), followed by DMAP (0.802 g, 6.62 mmol) and stirred overnight at RT. The mixture was quenched with water and extracted with EtOAc. After usual aqueous work-up and chromatographic purification, 0.3 g (6%) of prodrug **I-HI-NOPDI**. ¹H-NMR data is consistent with the expected structure, MS (CI)⁺ *m/z*: 376 [M+H]⁺.

Example 112

Synthesis of NO-releasing prodrug of paracetamol (**L-HI-NOMWa**):

This prodrug was synthesized as shown in Scheme 1A, Method D. Thus, to a solution of chlorocarbonyl isocyanate (0.701 g, 6.622 mmol) in benzene (5 mL) at 0 °C was added a solution of paracetamol (1 g, 6.622 mmol) and stirred at 0 °C for 1 h. To this was added a

solution of **1-2b** (1.21 g, 6.622 mmol) and TEA (1 mL) in THF (5 mL), and stirred overnight at RT. After usual aqueous work-up and chromatographic purification, 90 mg (3%) of prodrug **I-HI-NOPMa** was obtained. ¹H-NMR data was consistent with the expected structure. MS: (ES)⁺ m/z 418 (M+H)⁺.

5 Example 113

Synthesis of NO-releasing prodrug of paracetamol (**I-HI-NOP03**):

This prodrug was synthesized from paracetamol (2.0 g, 13.24 mmol) according to the procedure described in Example 114 (see Scheme 14, Method C). After usual workup, the crude product was purified by column chromatography to afford 1.0 g (20%) of prodrug **M11-NOPD3**. ¹H-NMR (500 MHz, CDCl₃): δ 2.11 (s, 3H), 2.91 (t, 2H, J = 6.5 Hz), 3.06 (t, 2H, J = 6.5 Hz), 3.49 (t, 2H, J = 6.5 Hz), 4.75 (t, 2H, J = 6.5 Hz), 7.05 (d, 2H, J = 9.0 Hz), 7.54 (d, 2H, J = 9.0 Hz). MS (ES)⁺ m/z 376 (M+H)⁺, 393 [M+K]⁺.

Example 114

15 Synthesis of NO-releasing prodrug of metronidazole (TMM-NOPD6):

This prodrug was synthesized in two steps as shown in Scheme 14, Method C.

Step 1: To a suspension of metronidazole (5 g, 29.22 mmol) in chloroform (100 mL) was added CDI (5.21 g, 32.2 mmol) and stirred overnight at RT. The reaction mixture after usual aqueous work-up, gave 7.66 g (98 %) of the imidazo[1,2-a]pyridine. ¹H-NMR data was consistent with the expected structure. MS (ES)⁺ m/z: 266 (M+H)⁺.

Step 2: To a solution of **UrSTE** (2.68 mmol) and TEA (1.08 g, 10.72 mmol) in DCM (10 mL) at 0 °C was added the imidazolide of metronidazole (0.78 g, 2.95 mmol) and stirred at RT for 48 h. The reaction mixture was quenched with water and extracted with DCM. After usual aqueous work-up and chromatographic purification 50 mg (4.3%) of **I-HI-NOPD6** was obtained. ¹H-NMR (500 MHz, CDCl₃): δ 2.50 (s, 3H), 2.80 (t, 2H, J = 6.3 Hz), 2.96 (t, 2H, J = 6.6 Hz), 3.47-3.50 (m, 2H), 4.4 (t, 2H, J = 5.1 Hz), 4.58 (t, 2H, J = 5.1 Hz), 4.70 (t, 2H, J = 6.6 Hz), 7.26 (s, 1H). MS (ES)⁺ m/z 395.99 (M+Bf).

Example 115

Synthesis of NO-releasing prodrug of budesonide (**I-HI-NOPD9**):

30 This prodrug was synthesized from budesonide (0.5 g, 1.16 mmol) according to the procedure described in Example 122 (see Scheme 14, Method C). After usual workup,

the crude product was purified by column chromatography to afford 0.25 g (33%) of prodrug 1-H(1-IVOPD). ¹H-NMR data was consistent with expected structure. MS (ES)⁺ Wz: 655 (M+Hf,

Example 116

5 Synthesis of NO-releasing prodrug of 4-hydroxy-TEMPO (1-HI-NOPD10):

A solution of **LI-2b** (0.20 g, 1.20 mmol) and CDI (0.195 g, 1.20 mmol) in chloroform (5 mL) was stirred at RT for 2 h, which was followed by the addition of 4-hydroxy-TEMPO (0.173 g, 1.00 mmol) and DMAP (0.122 g, 1.00 mmol). The mixture was refluxed for 2 d, then purified by column chromatography to afford 110 mg (27 %) of **1-HI-NOPD10** as a red oil. MS: EI⁺ m/z 398 [M+Hf, 420 [M+Na]⁺.

10

Example 117

Synthesis of NO-releasing prodrug of edaravone (1-HI-NOPD11):

To a solution of edaravone (0.87 g, 5 mmol) in acetonitrile was added KF-AcO₃ (66 g) and, after thorough mixing, **LI-0a** (2.8 g, 10 mmol) was added. The mixture was agitated for 20 h. After usual aqueous work-up and chromatographic purification, 70 mg (4%) of the intermediate bromide was obtained as a reddish-yellow oil. ¹H NMR (CDCl₃, 500 MHz); δ 2.28 (s, 3H), 3.00-3.10 (m, 4H), 3.59 (t, 2H, J = 5 Hz), 4.34 (t, 2H, J = 6.5 Hz), 5.5 (s, 1H), 7.4 (t, 2H, J = 1 Hz), 7.69 (s, 3H, J = 1 Hz). MS: ES⁺ m/z 375 [M+Kf, 397,0 [M+Na]⁺.

15

20 To a solution of the above bromide (0.05 g, 0.134 mmol) in acetonitrile (1.5 mL) was added Ag₂O (0.027 g, 0.160 mmol) and stirred for 20 h. After usual aqueous workup and purification 0.025 g (53 %) of **1-HI-NOPD11** was obtained as a brown gum. ¹H NMR (CDCl₃, 500 MHz); δ 2.28 (s, 3H), 2.90 (t, 2H, J = 6.5 Hz), 3.10 (t, 2H, J = 6.5 Hz), 4.33 (t, 2H, J = 6.0 Hz), 4.63 (t, 2H, J = 6.5 Hz), 5.5 (s, 1H), 7.60-7.63 (bs, 2H), 7.65-7.67 (bs, 3H). MS; ES⁺ m/z 356 [M+Kf].

25

30

Biological Example 1:

Screening of prodrugs and mutual prodrugs of anticonvulsants

Most of the prodrugs and mutual prodrugs of anticonvulsants described in, *Ms*
 invention were evaluated at National Institute of Neurological Disorders and Stroke
 5 (NINDS), National Institute of Health (NIH), under their Antiepileptic Screening
 Program (ASP).

Test 1 is an initial screening for anticonvulsant activity in the Maximal
 Electroshock Test (MES) and Subcutaneous Metazol Seizure Threshold Test (scMET)
 10 models combined with an initial assessment of toxicity (TOX) in mice via *Ip.* injection
 (see further explanation below). The data for each condition is presented as N/F, where N
 = number of animals protected from seizure and F = number of animals tested. For test of
 toxicity, N = number of animals displaying toxic effects and F = number of animals
 tested. Any deaths occurring during the test were recorded.

15 Maximal Electroshock Test (MES); The MES is a model for generalized tonic-
 clonic seizure and provides an indication of a compound's ability to prevent seizure
 spread when all neuronal circuits in the brain are maximally active. These seizures are
 highly reproducible and electrophysiologically consistent with human seizures. For all
 tests based on MES convulsions, 60 Hz of alternating current (50 μ A in mice) is
 20 delivered for 2s by corneal electrodes, which have been primed with an electrolyte
 solution containing an anesthetic agent (0.5% tetracaine hydrochloride). Mice were tested
 at various intervals following doses of 30, 100 and 300 mg/kg of test compound given by
i.p. injection of a volume of 0.01 mL/g. Other doses can be used if indicated by
 previously known pharmacology. An animal is considered "protected" from MES-
 25 induced seizures upon abolition of the hind-limb tonic extensor component of the seizure.

Subcutaneous Metazol Seizure Threshold Test (scMET): Subcutaneous
 injection of the convulsant metrazol produces clonic seizures in laboratory animals. The
 scMET test detects the ability of the test compound to raise the seizure threshold of an
 30 animal and thus protect it from exhibiting a clonic seizure. Animals were pretreated with
 various doses of the test compound given by *Ip.* injection. At the previously determined

Time to Peak Effect (TPE) of the test compound, the dose of metrazol which will produce convulsions in 97% of animals (CD_{97} : 85 rag/kg in mice) was injected into a loose fold of skin in the midline of the neck. The animals were placed in isolation cages to minimize stress and observed for the next 30 minutes for the presence or absence of a seizure. An episode of clonic spasms, approximately 305 seconds, of the fore and/or hind limbs, jaws, or vibrissas is taken as the end point. Animals which do not meet this criterion were considered protected.

Acute Toxicity - Minimal Motor Impairment (MMI): To assess a compound's undesirable side effects (toxicity), animals were monitored for overt signs of impaired neurological or muscular function. In mice, the rotorod procedure is used to disclose minimal muscular or neurological impairment. When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal can maintain its equilibrium for long periods of time. The compound is considered toxic if the animal falls off this rotating rod three times during a 1-min period. In addition to MMI, animals may exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of placing response and changes in muscle tone.

Compounds that were active in Test 1 (mice i.p.) were further screened in Test 2 (rat p.o.). Compounds failing activity in Test 2 (rat p.o.) were selected for secondary evaluation (i.e., Test 3, Rat P.O. quantitation) as explained below.

Secondary Evaluations All quantitative *in vivo* anticonvulsant/toxicity evaluations of the active compounds were conducted at compound's time of peak pharmacodynamic activity (TPE). Groups of at least 8 rats received various doses of the candidate compound until at least two points were established between the limits of 100 percent protection or toxicity and zero percent protection or minimal toxicity. The 95 percent confidence limits, slopes of the regression lines and standard errors of the slopes were calculated for each quantitative determination. Rats received test compounds orally.

Test 1 screening results are presented in Table 1, Compound I-CA-MPB24 was active in both MES and scMET models and was shown to be safe-toxic. However, some compounds were active in both MES and scMET models and were also shown to be

toxic The compounds (Le., I-A1~PD4, I-AA-MPD12, I-CA-MPD23, I-A1-PD5, X-A1-NOPD3, I-CA-MPD24, I-A1-PD15, I-CA-MPD25, and I-AA-MPD11) that are shown to be active in MES but showed no or mild toxicity were selected for Test 2 screening and those results are presented in Table 2.

- 5 Three of the compounds (i.e., I-A1-PD4, I-AA-MPD12, and I-A1-NOPD3) were considered for secondary evaluation, where quantification of their antiepileptic activity and neurotoxicity in rats (p.o.) was carried out. This secondary evaluation determines the time to peak effect (TPE), neurotoxicity, median effective dose (ED₅₀) and biological response. The 95% confidence interval, the slope of the regression line, and Uae standard error are then calculated. The results of secondary evaluation (Test 3) are presented in Tables 3A and 3B.

Table 1: Primary Screening (Test 1) data for Anticonvulsant Activity and Neurotoxicity in Mice (test compound administered I.p.)

Compd	MES ^{a,b}		ScMET ^{a,c}		Rotarod Toxicity ^{a,d}	
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
I-A1-PD7	+(1/1)	-	+(1/1) ^e	-	+(2/4) ^d	-
I-A1-PD8	++(2/3)	-	-	-	-	-
	+(1/1)	+(1/1)	+(1/1)	-	+(4/4) ^f	-
I-A1-PD4	-	+++ (1/1)	-	-	-	-
	++ (1/7)	++ (3/3)	-	-	-	-
	+(2/5)	+(1/1)	-	-	-	-
I-AA-MPD12	-	++ (3/3)	-	-	-	-
	nd	++ (1/3) ^g	nd	nd	nd	nd
	-	+(1/1)	-	-	-	-
I-CA-MPD23	-	++ (1/3) ^h	-	-	-	-
	-	+(1/3)	-	-	-	-
I-A1-PD13	+(1/1)	-	+(1/1)	-	+(1/4)	-
I-A1-PD5	+(1/1)	-	+(3/5)	-	+(3/4) ⁱ	-
I-A1-PD6	+(1/1)	-	+(1/1)	-	+(4/4) ^j	-
I-A1-PD10	-	-	-	-	++ (8/8) ^y	nd

I-AA-MPP13	-	-	+0/1)	-	+ (4/4)»	-
I-AI-NOPDI	++ (1/3) ^k + (1/1)	-	- + (3/1)	-	- + (4/4) ^f	-
I-AI-NOPD3	-	++(1/3) + (M)	++ <i>cm I</i> -	-	+++ (1/4) -	-
I-CA-MPD24	-	++(3/3) ++(3/3) ^h -H- (3/3) ^m	-	-	-	-
I-AI-PD15	+	++(2/3) + (1/1)	-	-	-	-
I-GA-MPD25	+	++(2/3) + (1/1)	-	-	-	-
I-AA-MPDU	-	++(3/3) + (1/1)	-	-	- + (1/4)	-

^aKey; +++ ~ activity or toxicity at 30 mg/kg, ++ ~ activity or toxicity at 100 mg/kg, +

* activity or toxicity at 300 mg/kg, - ~ no activity or no toxicity at 300 mg/kg

[^]Maximal electroshock seizure test Subcutaneous pentyltetrazole seizure test

5 ^dNeurological toxicity (number of animals exhibiting toxicity/number of animals

tested). ^e(number of animals protected/number of animals tested), ^mnot determined

^fLoss of righting reflex. ^gAt 6 hours after dosing. ^hAt 2 hours after dosing- *Unable to

maintain rotorod. ⁱDeath. ^kAt 0.25 hours after dosing. [^]Myoclonic jerks. ^mAt 6 hours after

dosing.

10 Table 2: Screening (Test 2) data for Anticonvulsant Activity and Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose (mg/kg)	Time (h)	MES ^{a,b}	Toxicity ^{a,d}
I-A1- PD4	30	0.50	0/4	0/4
		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-AA- MPD12	30	0.50	0/4	0/4
		1.00	0/4	0/4
		2.00	1/4	0/4
		4.00	3/4	0/4
I-CA- MPD23	150	2.00	4/4	0/4
		4.00	4/4	0/4
		6.00	4/4	0/4
		8.00	4/4	0/4
I-A1- PD5	50	0.50	0/4	0/4
		1.00	0/4	0/4
		2.00	1/4	0/4
		4.00	1/4	0/4
I-A1- NOPD3	30	0.50	0/4	0/4
		1.00	2/4	0/4
		2.00	1/4	0/4
		4.00	4/4	0/4
I-CA- MPD24	30	0.50	0/4	0/4
		1.00	2/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-A1- PD15	30	0.50	0/4	0/4
		1.00	1/4	0/4
		2.00	3/4	0/4
		4.00	4/4	0/4
I-CA- MPD25	30	0.50	0/4	0/4
		1.00	3/4	0/4

		2.00	4/4	0/4
		4.00	2/4	0/4
I-AA-MPDII	30	0.50	0/4	0/4
		1.00	2/4	0/4
		100	1/4	0/4
		4.00	4/4	0/4

^Maximal electroshock seizure test, ^ (number of animal protected/number of animal tested). Neurological toxicity, d_{GBMT} (number of animals exhibiting toxicity / number of animals tested).

- 5 Table 3Ai Screening (Test 3) data for Anticonvulsant Activity (Time to Peak Effect) and Neurotoxicity in Rats (test compound administered p.o.)

Compd	Dose (mg/kg)	Time (h)	Time to Peak Effect		Toxicity % (mg/kg)
			MES 8.0	ScMET ^{III} c (50 mSHSg)	
I-AI-PD4	10	4.0 6.0 8.0 24	4/4 3/4 2/4 0/4		
	30	0.25 0.5 1.0 2.0 4.0	2/4 2/4 2/4 2/4 4/4	1/4 0/4 2/4 1/4* 0/4	0/4 (100) 0/4 (100) 0/4 (100) 0/4 (100)
I-AA-MPD12	15	6.0 8.0	2/4 1/4		

	30	0.5	0/4		
		1.0	0/4	1/4	0/4 (50)
		2.0	1/4	0/4	0/4 (50)
		4.0	3/4	0/4	0/4 (50)
		6.0	4/4	1/4	0/4 (50)
		8.0	4/4	2/4	0/4 (50)
		24	2/4	0/4	0/4 (50)
		8.0			1/8 (100) ^h
I-A1-NOPD3	30	0.25			0/8 (500)
		0.5			0/8 (500)
		1.0			0/8 (500)
		2.0	1/4	0/4	0/8 (500)
		4.0	3/4	0/4	0/8 (500)
		6.0	3/4	1/4	1/8 (500)
		8.0	4/4	3/4	0/8 (500)
		24	3/4	1/4	

^aMaximal eledroshock seizure test- "(number of amtnal protected/number of animal tested). Subcutaneous peotylenetetrazole seizure test. ^hNeurological toxicity, (sunibet of animals exhibiting toxicity (i.e., atoxia)/number of animals tested),
 5 i teafh following continuuous seizure ^hPopcorn effect and cotttiouons seizure activity. ^hMUd ataxia only.

Table 3B: Screening (Test 3) data for Anticonvulsant Activity (ED₅₀ and Biological Response and ED₅₀) in Rats (test compound administered p.o.)

Compd	ED 50 Values and Biological Response					
	Time c (h)	Dose (mg/kg)	MES ^{a,b}	ED ₅₀	95% Confidence Interval Low/High	Slope/Std. Er

I-A1-PD4	4	1.9	0/8	6.55	3.56/10.72	2.27/0.63
		3.8	4/8			
		7.5	4/8			
		15	7/8			
		30	7/8			
I-AA-MPD12	6	7.5	0/8	17.1	9.98/25.8	3.2/0.95
		15	5/8			
		30	7/8			
		60	7/8			
I-A1-NOPD3	8	3.8	3/8	10.1	2.99/17/44	1.61/3.15
		7.5	3/8			
		15	4/8			
		30	9/12			
		60	8/8			

^aMaximal electroshock; seizure test. ^number of animals protected/number of animal tested).

I-A1-PD4 is a simple prodrug of lamotrigine. For this prodrug, BD_{50} for the MES model, was determined to be 6.55 mg/kg and the time to peak effect was found to be 4.0 h after drug administration at doses of 10 as well as 30 mg/kg. This compound has shown moderate protection in scMBT models where one out of four animals were protected at 0.25 h and 2.0 h period and two out of four animals were protected at 1.0 h after administration of the drug at a dose of 50 mg/kg. For the toxicity analysis* none of the animals given 100 mg/kg showed signs of toxicity.

I-AA-MPP12 is a mutual prodrug of lamotrigine and gabapentin ethyl ester. For this compound, ED_{50} for the MES model was found to be 17 mg/kg and the time to peak effect was found to be 6.0-8.0 h at a dose of 30 mg/kg and indicated a significant extension protection (2 out of 4 animals were still protected) at 24 h after drug administration. Surprisingly, this compound, although less potent than lamotrigine, has exhibited significant extension in the duration of protection. At 50 mg/kg, none of the animals exhibited toxicity. However, at 100 mg/kg, one of eight animals exhibited mild ataxia.

I-A1-N0PD3 is a NO-releasing prodrug of lamotrigine. For this prodrug, ED₅₀ for the MES model was determined to be 10.1 mg/kg and the time to peak effect was found to be at 5.0 h at a dose of 30 mg/kg and revealed a significant extension of protection (3 out of 4 animals were still protected) even at 24 h after drug administration. Surprisingly, this prodrug, although less potent than its parent drug, has exhibited significant extension in the duration of protection. At 50 mg/kg, this compound has also exhibited significant protection (3 out of 4 animals were protected at 8 h after drug administration) in scMET rat model. For the toxicity analysis, only one in eight animals exhibited toxicity at 6.0 h time point at a dose of 500 mg/kg. At other time points (ie., 0.25 h, 0.5 h, 1.0 h, 2.0 h, 4.0 h, 8.0 h after drug administration), none of the animals (0/8) exhibited any significant toxicity at the high dose of 500 mg/kg.

Biological Example 4

The pharmacological experiments on NO-releasing aspirin prodrugs were carried out by following the procedures described herein:

15 Animals and Procedures:

Male or female Sprague-Dawley rats weighing 150-200 g were used in the study. The rats were fed normal standard laboratory chow and maintained under standard conditions (room temperature of 22 ± 2 °C; 50 ± 10 % relative humidity; artificial light 06:00 to 18:00). All experimental procedures mentioned below are approved by institutional animal research committees and were performed in accordance with standard guidelines for the treatment of animals.

Sample preparation and Standard curve;

HPLC: Waters Alliance analytical HPLC equipped with 2996 PDA detector and Empower software were used to analyze the samples.

25 HPLC Column: Waters X-Terra RP-18 analytical column, 150 X 3.9 mm, 5 µm

HPLC Method; Flow; 1 mL/min, detector set at 210 nm and at Maxplot (210-400 nm range). Solvent A: Acetonitrile; Solvent B: 0.1% TFA in water, Elution method: A linear gradient of 0-100% A.

Plasma samples were processed by transferring 75 µL quantity of blood into a test tube containing 250 µL acetonitrile, vortex-mixed and centrifuged at 1000 g for 5 min. 200 µL of supernatant was then taken and diluted to 2 times with acetonitrile. 100 µL of

the sample was injected into HPLC for analysis. Salicylate standard curves were generated using acetonitrile as solvent in the working range of 1-100 $\mu\text{g}/\text{M}$,

Pharmacokinetic parameters were calculated using WinNon-m software (4.1 version). C_{im} , T_{max} , AUC 0-24, AUC 0-Mfinity, and $T_{1/2}$ characterized and each curve generated following oral treatment.

In Vitro Plasma stability;

The rationale is that these prodrugs would be hydrolyzed in-vivo before, during or after absorption to release the corresponding free drugs. Therefore, we tested whether the test compounds (I-CI-NOPD6, I-CI-NOPD4, I-CI-NOPD5A) released parent drug in rat plasma at 37 °C after 30 minutes incubation. The compounds were extracted back into acetonitrile with rigorous vortex. The results suggested that all prodrugs tested except I-CI-NOPD6 were found to be converting to the expected metabolite (salicylate) of the parent drug (aspirin) as revealed by HPLC analysis. Even aspirin was completely metabolized to salicylate after 30 minutes of incubation with rat plasma indicating that all the test compounds released aspirin, which in turn converted into salicylate.

Pharmacokinetic studies:

The oral pharmacokinetics of the test compounds, I-CI-NOPD6, I-CI-NOPD4, I-CI-NOPD5A and I-CI-NOPD5B was done in rats and the release profiles of salicylate from these compounds were analyzed by HPLC and the results were presented in Figure 1 and Table 4. Overnight fasted rats were fed with 35 mg/kg equivalent doses of aspirin and test compounds. Blood was collected from orbital plexus of test animals at various time points up to 24 hrs. As shown in Figure 1 the test compounds I-CI-NOPD4 and I-CI-NOPD5B indicated unexpected drug release profiles wherein the salicylate is released in a sustained and controlled manner starting from 1 hour through 12 hours. For I-CI-NOPD5B, the plasma salicylate concentration was maintained between 50 and 75 $\mu\text{g}/\text{mL}$ during this extended period of over 11 hours. This kind of plasma concentrations of the drug can result in significant extension of duration of action. For I-CI-NOPD4 also, the plasma salicylate concentration was maintained between 35 and 50 $\mu\text{g}/\text{mL}$ during an extended period of over 11 hours. Although aspirin absorption (Figure 1) was highest during 0.5 - 6.0 hrs (during which period much of the damage to the gastrointestinal tract

of the subject occurs due to high concentrations of the drug), plasma salicylate concentration for aspirin and I-C1-NQPD4 were comparable during the period from 8 through 24 hours. Such sustained release profile of active drug from the prodrug is expected to cause negligible or insignificant gastrointestinal damage as the plasma concentration of the drug never reaches to the toxic levels. Similar release profile was observed with I-C1-NQPD5A but for a shorter period of time. Unexpectedly, we have also observed as recorded in Table 4, nearly equal drug AUC values for aspirin and I-C1-NQPD5B (i.e., 923.63 ± 182.08 for aspirin vs 951.98 ± 11.58 for I-C1-NQPD5B) which indicates that the prodrug is as bioavailable as its parent drug, but prodrug does not cause gastric damage. Surprisingly, neither the prodrug nor the salicylate was found in the plasma of the animals fed with I-C1-NQPD6 (data not included in the graph) at any point of time tested, the reasons for which are not known.

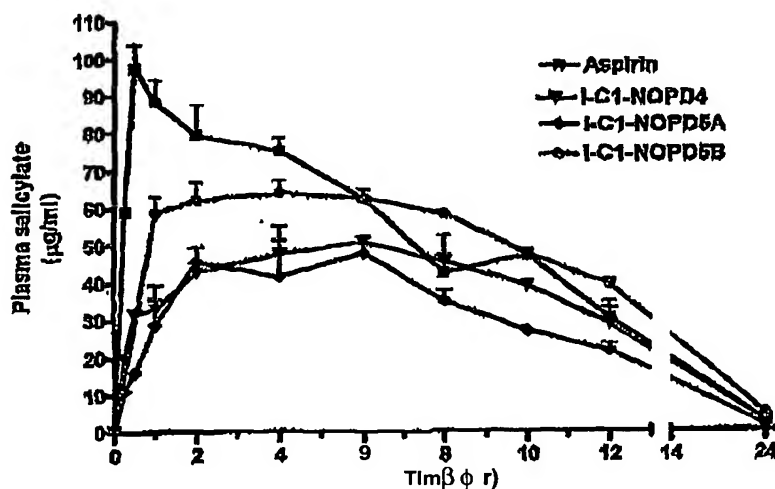


Figure 1. Plasma salicylate profile of aspirin and its NOrel basing prodrugs, The data values are expressed as Mean \pm S_{RM}, n=3-4 animals, the data values at time points 6 and 10 hours is an average from two animals only.

Table 4. Comparison of pharmacokinetic parameters of aspirin and its nitro derivatives

parameter**	Aspirin	I-C1-NQPD4	I-C1-NQPD5A	I-C1-NQPD5B
C _{max} * (µg/mL)	98.67 \pm 12.64	53.24 \pm 6.39	50.14 \pm 10.12	66.08 \pm 3.31
T _{max} (h)	0.50 \pm 0.00	4.66 \pm 0.57	3.00 \pm 0.57	4.00 \pm 0.81

AUC(MiH (h.µg/ml)	905.84 ± 173.14	749.36*69.38	557.80 ±97.65	922.89 ± 12.50
AUCm ₁ (h.µg/ml)	923.63 ± 182.08	772.17*75.68	565.30 ±96.78	951.98 ± 11.58
T _{1/2} (h)	3.58 ±0.42	3.984 ±0.25	3.35 ±0.32	4.14 ±0.24

*The data values are mean ± SEM, n³⁻⁴

Ulcerogenic activity:

Gastrointestinal ulceration is a serious side effect associated with NSAIDs. The clinical uses of potent NSAIDs are greatly limited by its gastrointestinal toxicity. We tested ulcerogenic potential of the test compounds, KU-NOPD6, 1-CI-NOPD4, 1-CI-NOPD5A, and X-CI-NOPD5B in rats. Overnight fasted rats were given orally 100 mg/kg equivalent doses of aspirin and prodrugs (in the case of 1-CI-NOPD5A and 1-CI-NOPD5B, 200 mg/kg equivalent doses were administered). The animals were sacrificed at 3 hours after drug administration. Stomachs of treated rats were separated, perfused with 10 ml of 2 % formalin, and then cut open over the greater curvature. The severity of the mucosal damage was then assessed on the basis of size (area) of the observed ulcers under surgical microscope with a square grid as per the established procedure (Takeuchi et al, J. Pharmacol. Exp. Ther. 1998, 286 (1), 115-121). Interestingly, none of the animals treated with the test compounds showed any signs of development of ulcers. However, severe haemorrhagic lesions (Mean ± S.E.M.; 2.7 ± 0.9 mm²) were seen in aspirin treated rats.

Anti-inflammatory activity:

Anti-inflammatory activity of test compounds was measured in carrageenan-induced rat paw edema model (Takeuchi et al, J. Pharmacol. Exp. Ther. 1998, 286 (1), 115-121). The activity of aspirin and test compounds (75 mg/kg equivalent dose of aspirin) is shown in Table 5. Aspirin at 75 mg/kg, p.o. exhibited anti-inflammatory activity from 1 hr through 6 hr with peak maximal activity at 4 hr. 1-CI-NOPD4 showed significant activity during the first two hours after drug administration but its activity was not as good as that of aspirin from 2 hr through 6 hr. Surprisingly, 1-CI-NOPD5A showed negligible anti-inflammatory activity at any time point tested (data not incorporated). We have not yet evaluated 1-CI-NOPD5B in this efficacy test.

Table 5

Compound	Rat paw edema (% inhibition)			
	Mean*	SEM, n = 6		
5	1 hour	2 hour	4 hour	6 hr
Aspirin	31.0*7.2	52.5 ±3.4	60.7±6.9	42.8±6.9
I-C1-N0PD4	42.4 ± 13,3	44.9 ± 12.9	243 ±7.7	8.6±5.1

10

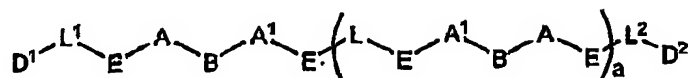
The results indicate the following:

1. Sustained release of the active drug over a period of 10-11 hours, which is good for twice daily dosage regimen, and
2. Exceptional gastrointestinal safety even at high equivalent doses of prodrugs compared to aspirin, which caused severe ulcers at equivalent doses.

15

We claim:

1. A compound of formula ϕ , novel intermediates in preparation thereof, or pharmaceutically acceptable salts thereof:



5

Formula (I)

wherein,

a is 0-2;

B independently represents a bond, $(CH_2)_b$, $(CKbCH_2O)_0$, S-S, S-S-O, S-SO₂ or S-S=NH;

10 b is 1-6; c is MOOO;

A and A' independently represent a bond, $(CH_2)_d$, 1,2-phenylene, 1,4-phenylene or 1,4-phenylene;

d is 1-8;

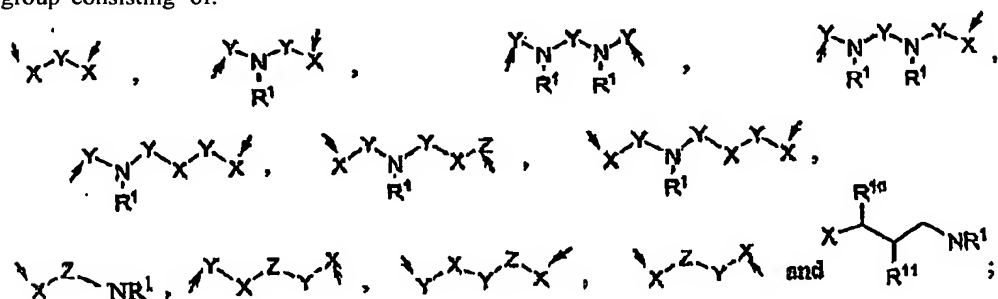
15 D¹ represents a therapeutic agent comprising one or more of the functional groups selected from the group consisting of -OH, -SH, -NHR¹, -CO₂H, -CONHR¹, -OCC(=O)KHR¹, -SO₂NHR¹, -OSO₂NHR¹, -N(R¹)SO₂NHR¹ and -N(R¹)SO₂NHR¹;

D² independently represents P¹, a peptide, protein, monoclonal antibody, vitamin, R², R³, R⁴, NO, NO₂, NONOate or any other nitric oxide-releasing group or molecule, a group of molecule comprising one or more of water-solubilizing functional groups, a polymer or

20 an amino acid;

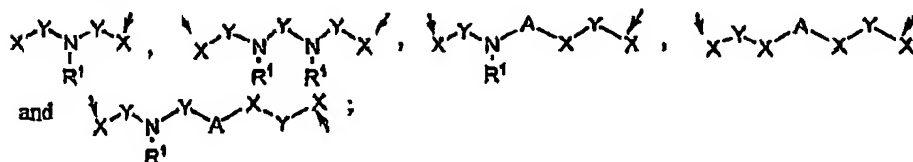
E independently represents CH₂ or a bond;

L¹ and L² independently represent a bond, O, S, NR¹, L, or a linkage selected from the group consisting of:



25

L is R¹² or a group with bonding in any direction, independently selected from the group consisting of;



X independently represents a bond, C, O, S, or NR^j

5 y independently represents a bond, C=O, C=S, S=O, SO₂, P(O)XR¹, or CH^y, wherein
ti is as defined;

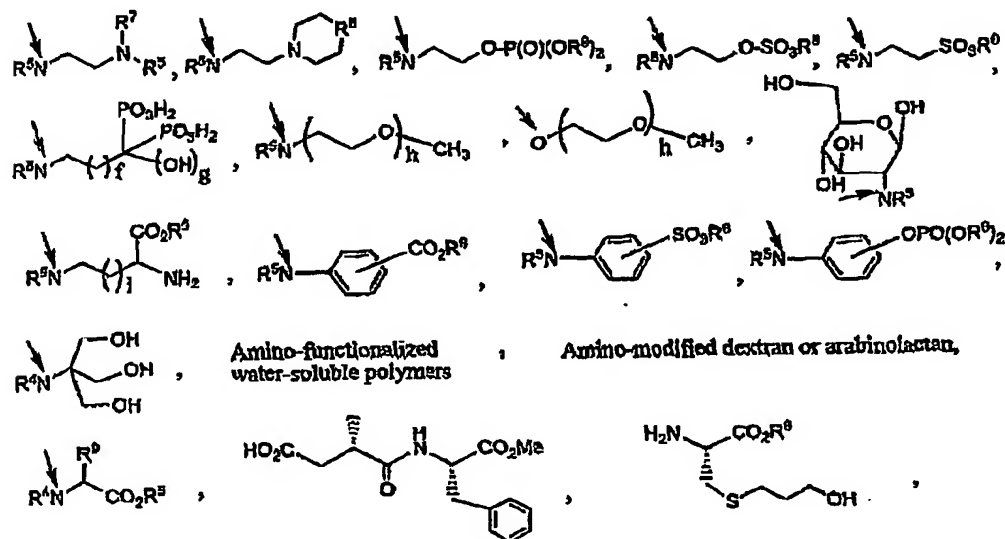
Z independently represents a bond, or (CH_j)_{J_j} wherein, j is 1-4;

R¹ independently represents a bond, H, (C₁-O-alkyl), substituted(C₁-C₅)alkyl, (C₁-C₄)aryl, aralkyl or M¹;

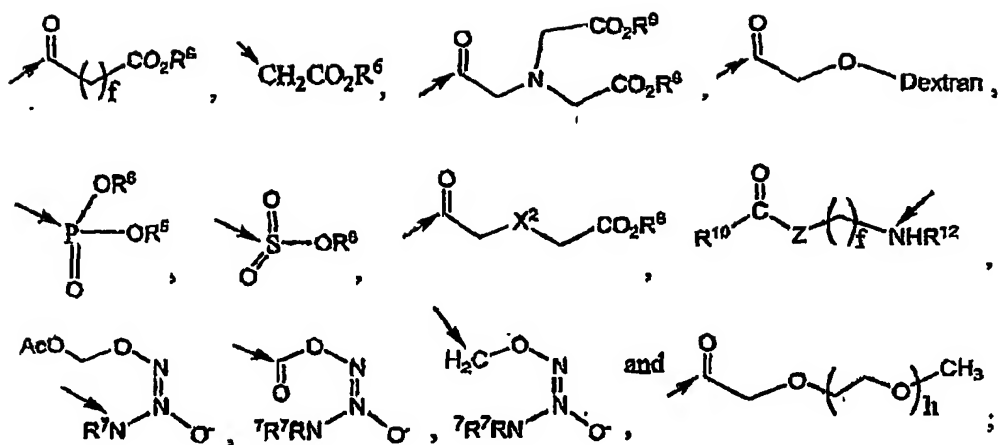
10 R² independency represents H₃NH⁺, or NHAc;

R^3 independently represents H, CO_2R^5 or $CH_2CO_2R^5$;

R⁴ independently represents H, OH, O-(C₁-C₆)alkyl, OM*, or a group selected from the group consisting of:



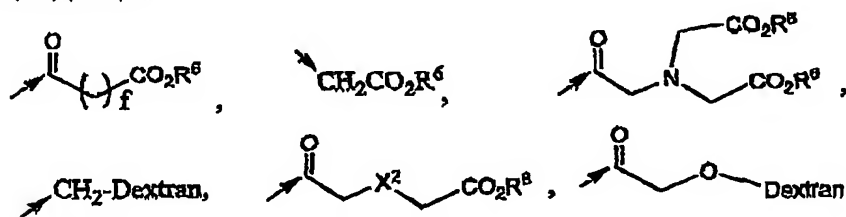
15



M independently represents Na, K or a pharmaceutically acceptable metal ion;

5 e = 1-3;

R^5 independently represents at each occurrence H, M^{++} , $(\text{C}_1\text{--C}_8)\text{alkyl}$, $(\text{C}_3\text{--C}_8)\text{cycloalkyl}$, substituted $(\text{C}_5\text{--C}_{14})\text{aryl}$, hetero $(\text{C}_2\text{--C}_{14})\text{aryl}$, $\text{C}(=\text{O})(\text{CH}_2)_f\text{CHR}^9\text{CO}_2\text{R}^5$, $\text{CH}_2\text{C}(=\text{O})\text{OR}^5$, $\text{P}(=\text{O})(\text{OR}^5)_2$,



10 X^2 independently represents O, S, SO, SO_2 , or NR^5 ;

R^6 independently represents H, Na^+ , K^+ or any other pharmaceutically acceptable metal ion, $(\text{C}_1\text{--C}_8)\text{alkyl}$, or $(\text{C}_3\text{--C}_8)\text{cycloalkyl}$;

R^7 independently represents at each occurrence same or different R^7 ;

R^8 independently represents CH_2 , O, NR^8 , S, $\text{S}=\text{O}$ or $\text{O}=\text{S}=\text{O}$;

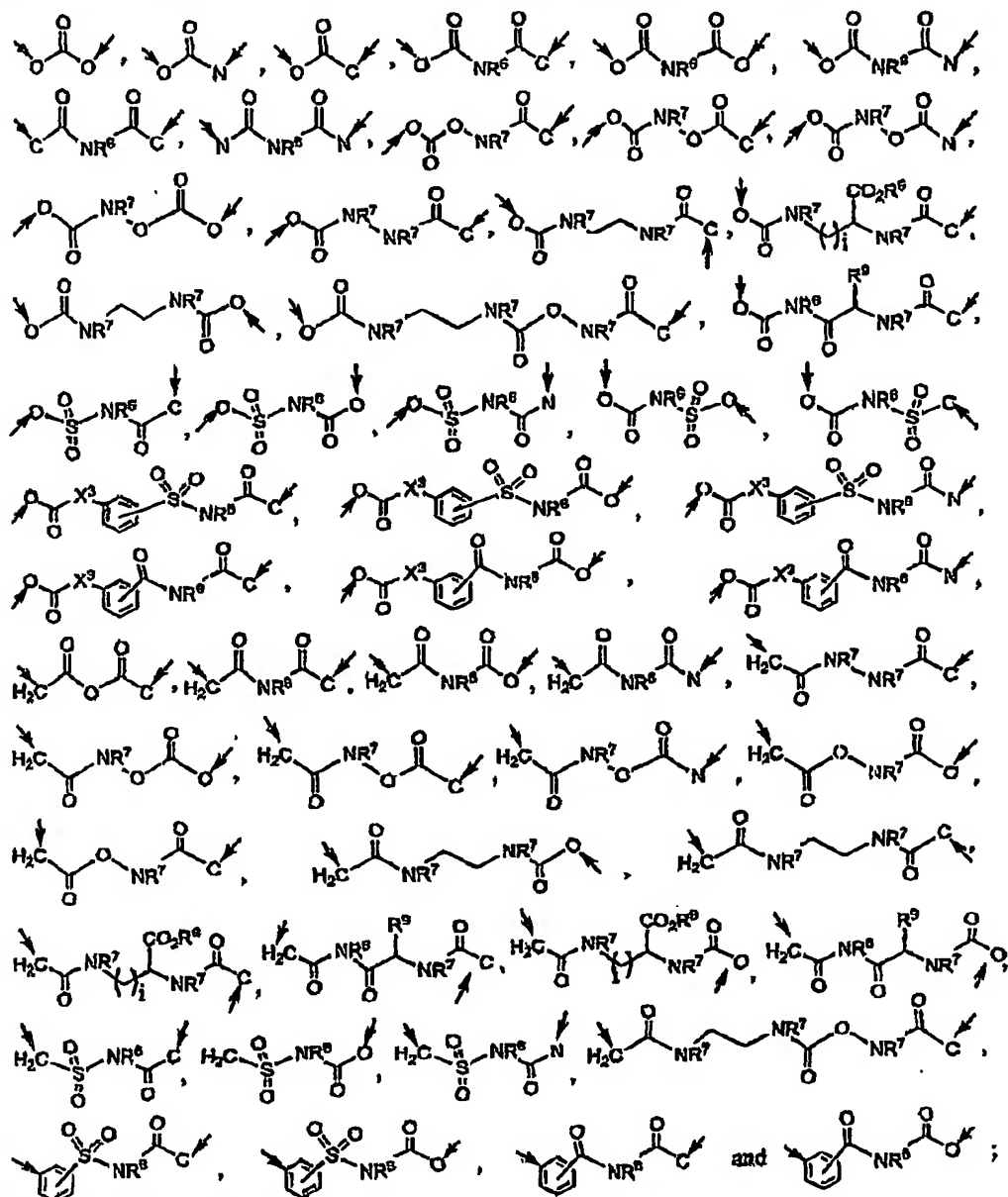
15 R^9 independently represents H, $(\text{C}_1\text{--C}_8)\text{alkyl}$ or an amino acid;

f is 0-6;

g is 0-1;

h is 1-2000;

R^{12} independently represents a group selected from the group consisting of:

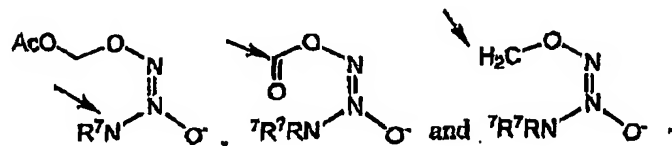


X^3 is independently O or NR^7 .

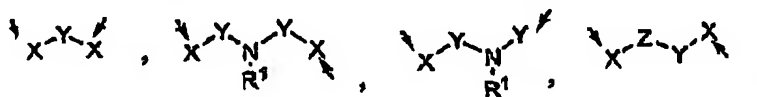
- 5 2. The compound according to claim 1, wherein a is 0.

3. The compound according to claim 1 wherein D² is a group or molecule comprising one or more water soluble functional groups selected from the group consisting of hydroxy-, amino, acylamino, carboxyl-, sulphate, sulfonate, phosphate, phosphonate, N-acylsulfonamide, N-acylsulfamate, N-acylcarbamate, N-acylcarbamate metallic salts* and amino acids to form water-soluble prodrugs.
4. The compound according to claim 2, wherein D² is selected from the group of amino acids consisting of Alanine, Arginine, Asparagine, Aspartic acid, Cysteine, Glutamine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, and Valine.
5. The compound according to claim 2 wherein D² is a polymer.
6. The compound according to claim 1 wherein the polymer is selected from the group consisting of dextran, modified dextran, arabinogalactan, polyamides, and polyethylene glycol.
7. The compound according to claim 6, wherein the polymer is a polyaminoacid selected from group consisting of poly(L-glutamic acid), poly(D-glutamic acid), poly(D-glutamic acid), poly(L-aspartic acid), poly(D-aspartic acid), poly(DL-aspartic acid), copolymers of the polyaminoacids and polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polycaprylic acid, poly(L-hydroxy-L-glutamine), dextran aldehyde, carboxymethyl dextran, arabinogalactan aldehyde, carboxymethyl arabinogalactate, and hyaluronic acid.
8. The compound according to Claim 5, wherein the polymer has a molecular weight of about 5000 to about 100,000 Daltons.
9. The compound according to Claim 5, wherein the polymer has a molecular weight of about 10,000 to about 50,000 Daltons.
10. The compound according to claim 2 wherein D² is a dipeptide.
11. The compound according to claim 2, wherein D¹ is a vitamin selected from the group consisting of Vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, nicotinic acid, nicotinamide, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D₂, vitamin D₃, vitamin D₄, vitamin E, menadione, menaquinone, and vitamin K₅.

12. The compound, according to claim 2, L^2 is O; A and A' are independently (CH[^]U-phenylsulfone, U-phenylone* or 1,4-phenylene; d is 1-4; B is S-S, S-S=O, S-SO₂ or S-S=NH; D² is NO, NO_a or a NONOate selected from the group consisting of:

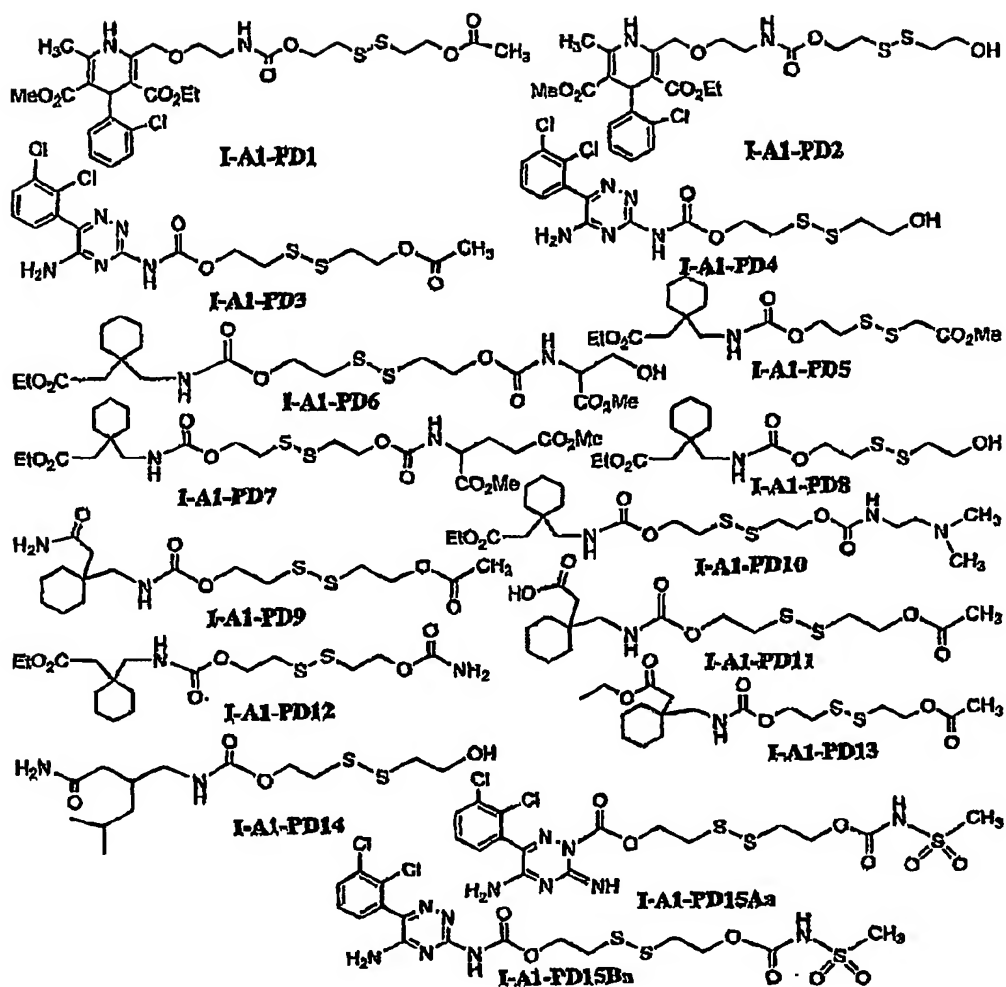


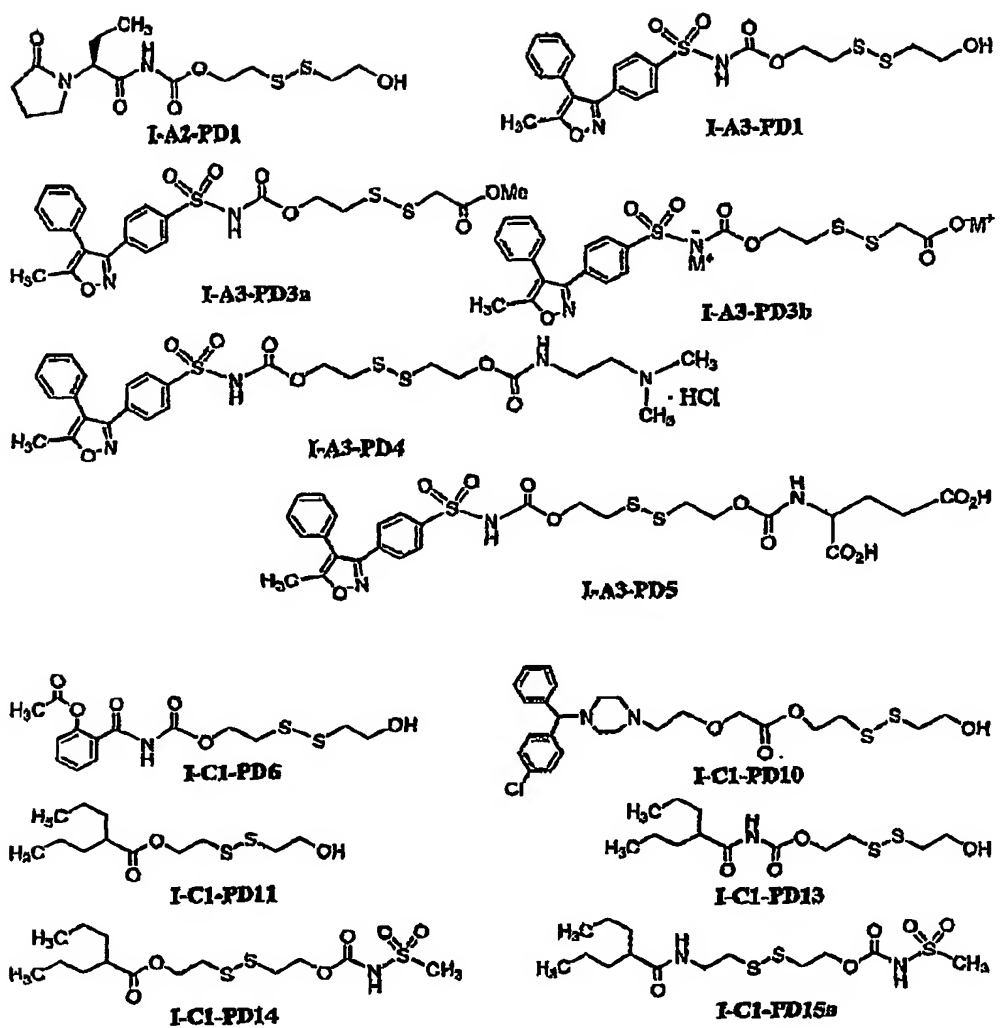
5 13. The compound according to claim 2, wherein L^2 is O; A and A' are CH₂; E is CH₂; B is a bond or (CH₂)₁₋₆; b is 1-6; a is O; D² is NO* and L¹ is a group selected from

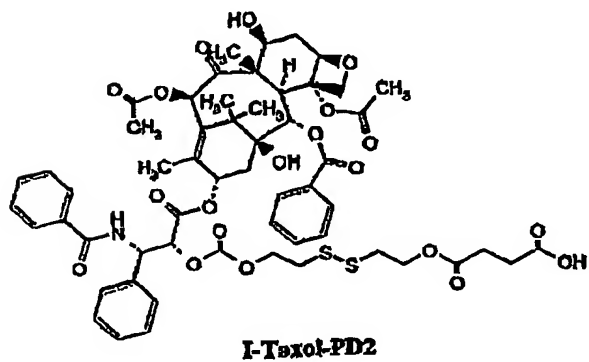
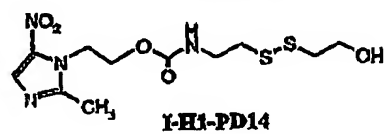
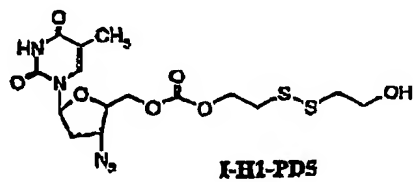
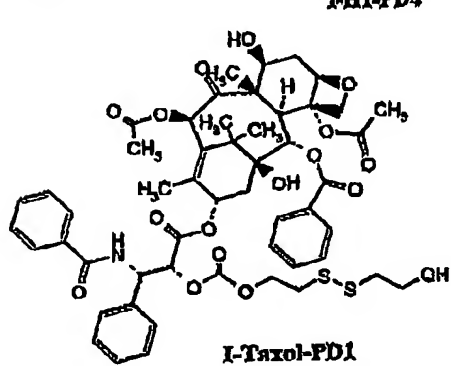
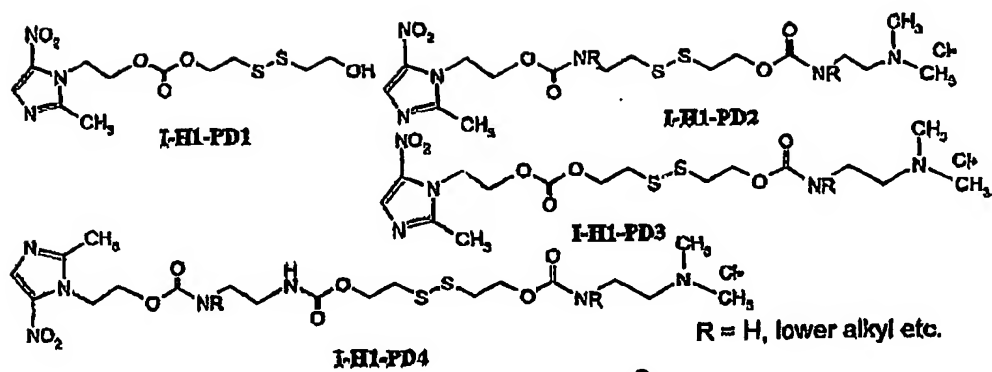


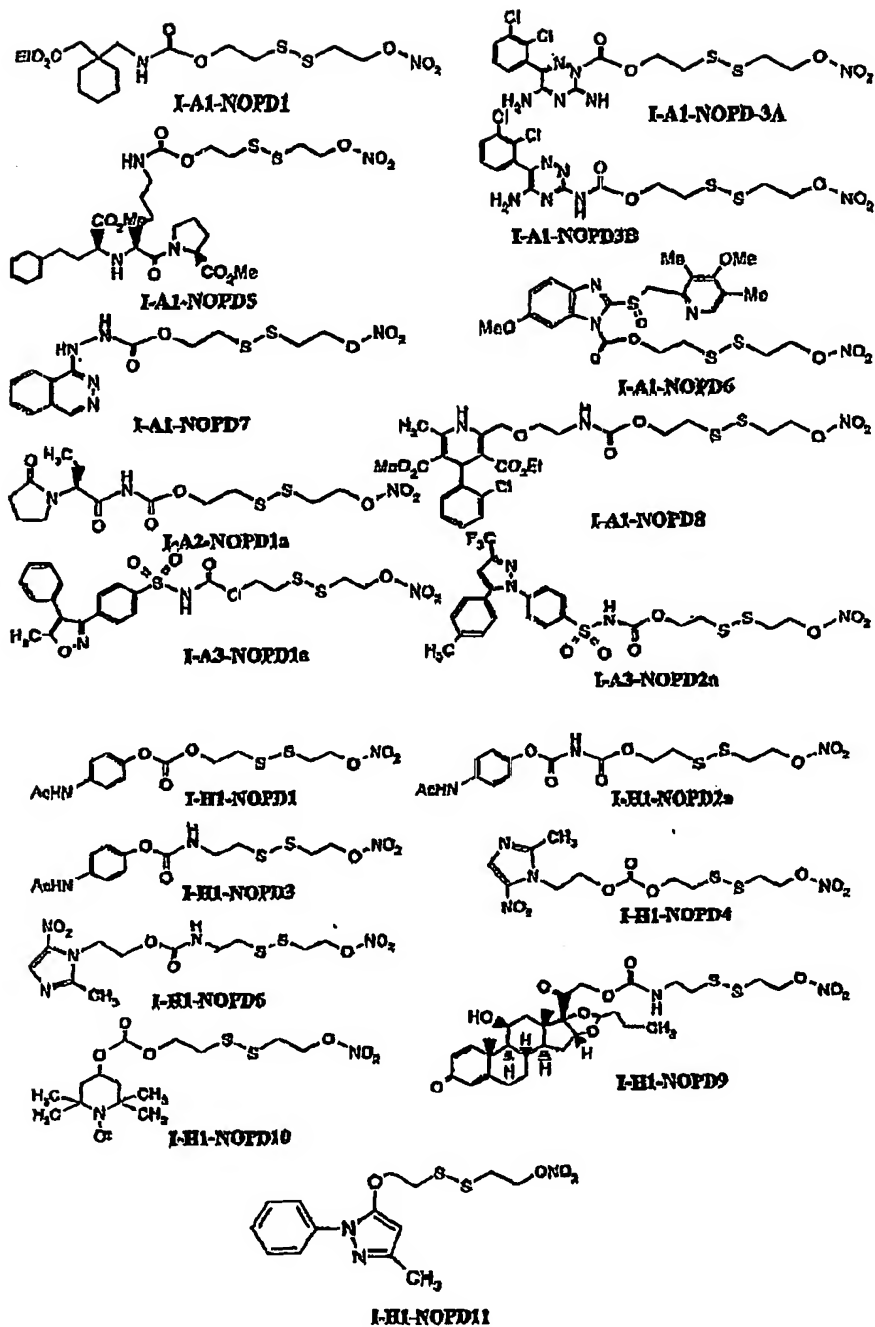
wherein, X is O, S or W; and Y and Z are as defined.

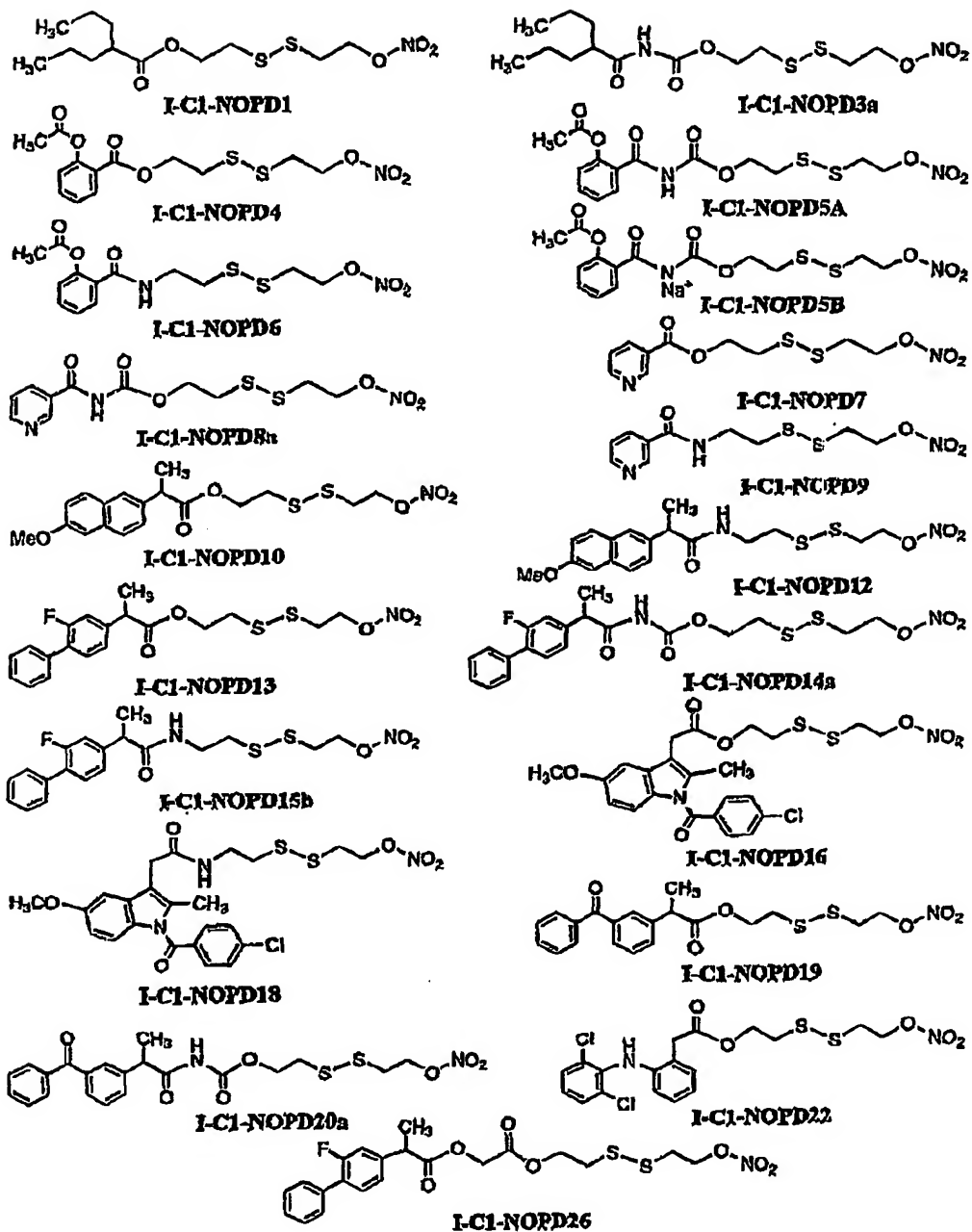
14. The compound according to claim 2, selected from the group consisting of:

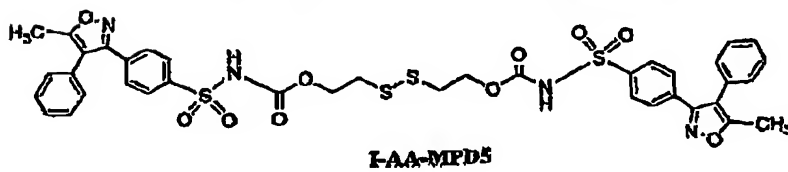
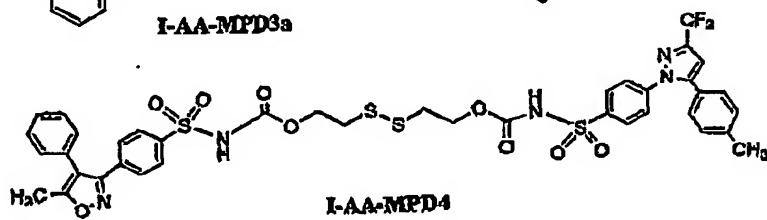
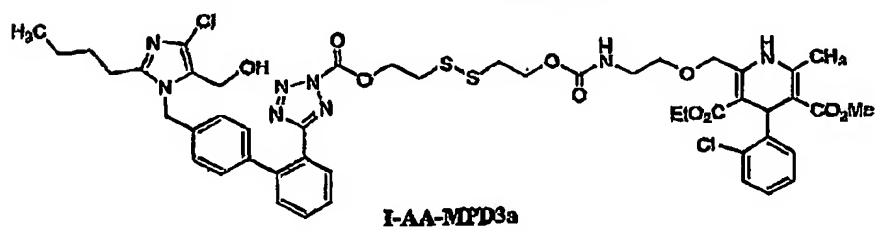
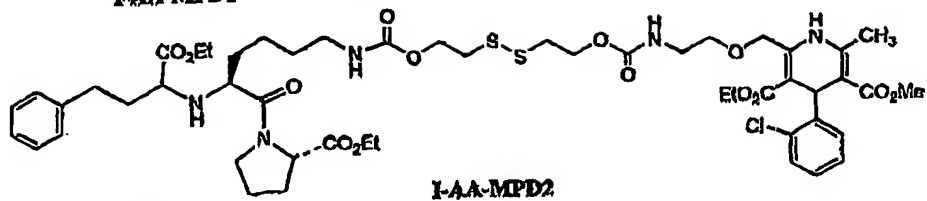
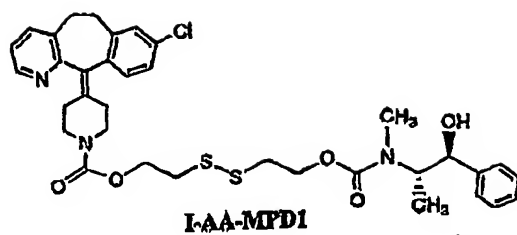


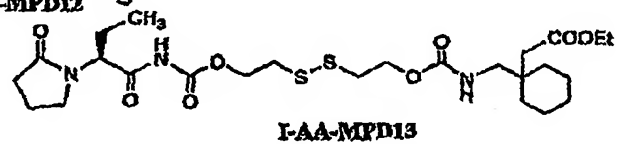
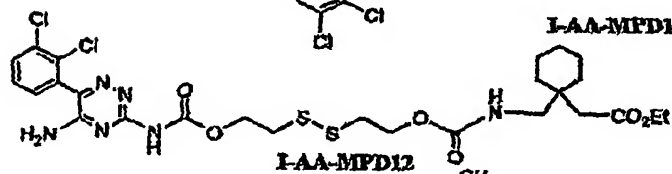
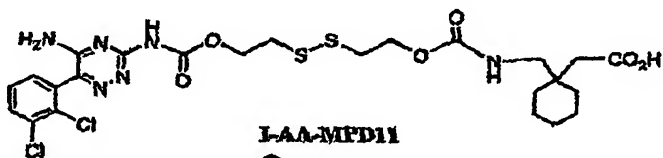
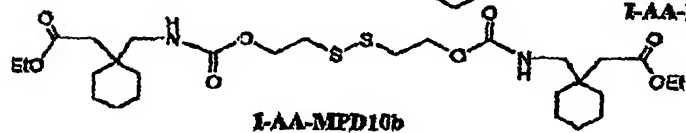
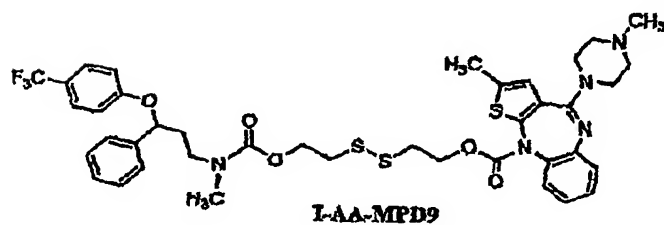
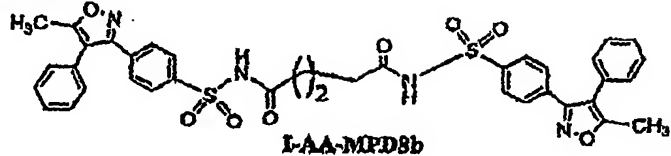
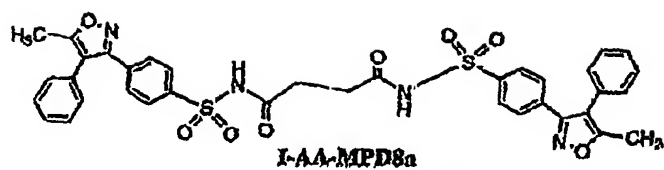


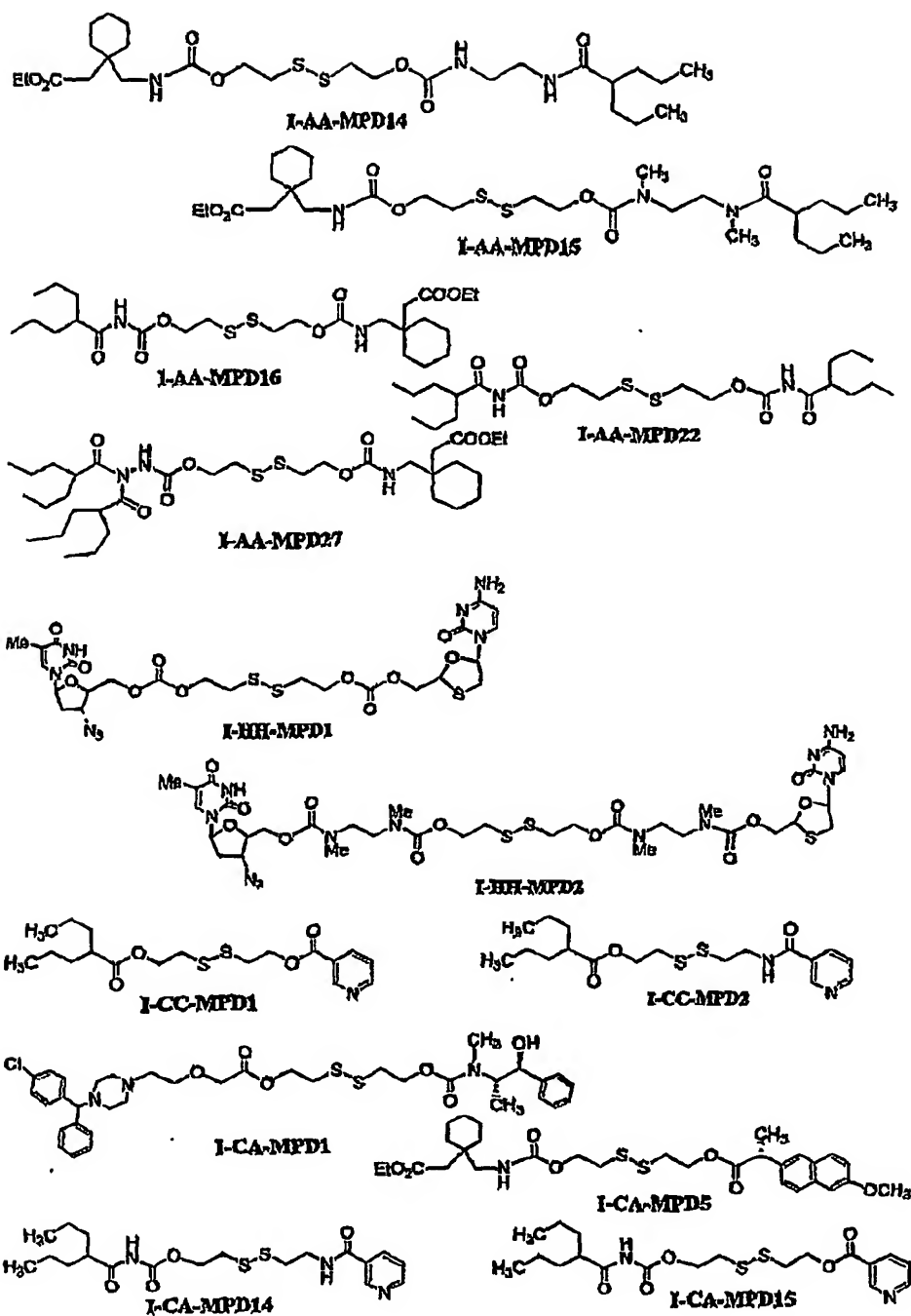


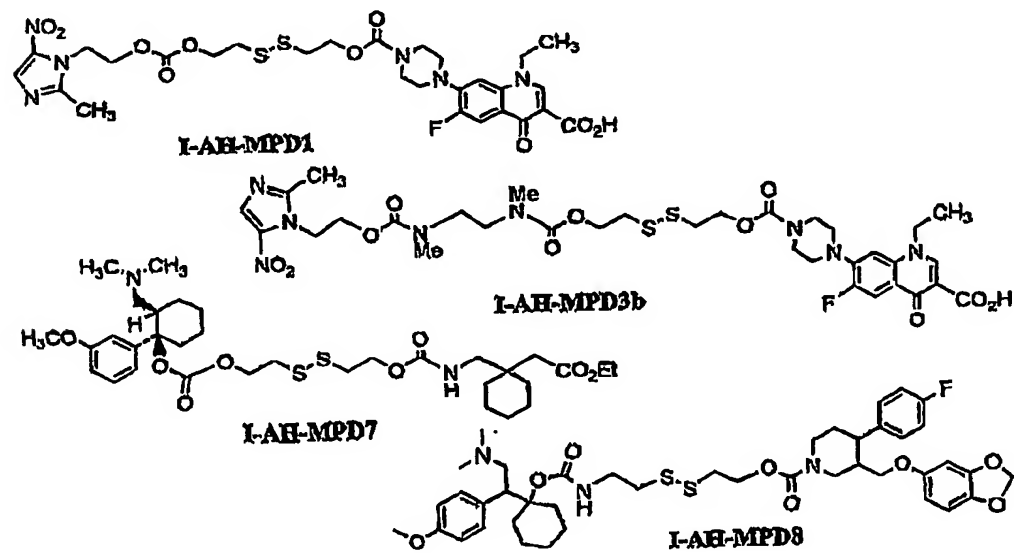
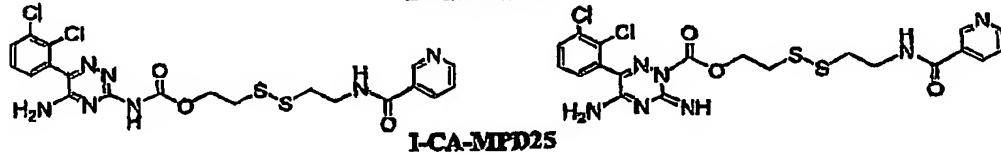
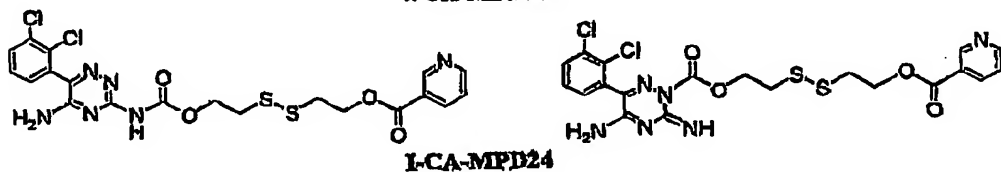
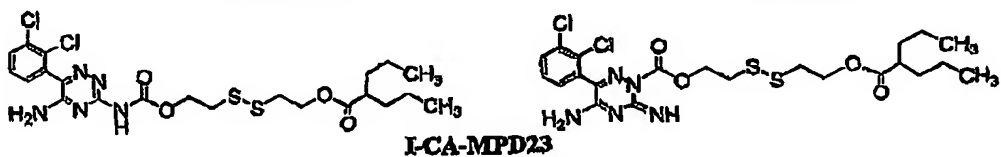
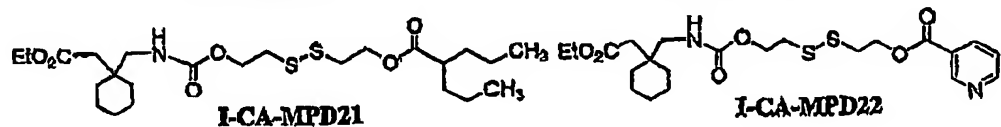
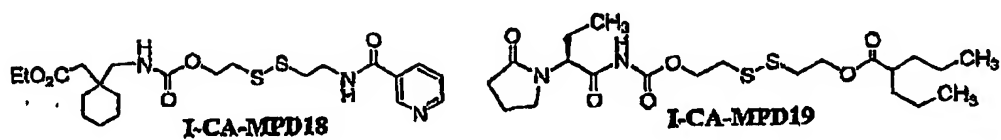












15. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 2, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.
16. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 14, or a pharmaceutical salt thereof and one or more pharmaceutically acceptable carriers, vehicles or diluents.
17. The compound as in claim 2, wherein D¹ and D* represent known and investigational amino-, hydroxyl-, carboxyl-, and keto- containing drugs compiled in drug databases comprising the Merck index, EMDbase, Prous Science's Integrity®, Prous Science Drugs of the Future™, and The Ensemble®.
18. The composition of claim 15 comprising therapeutically effective amount of pairs of drugs selected from; paclitaxel and Doxorubicin; Paclitaxel and Mitomycin C; Paclitaxel and P-aminocaproic acid; 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP), 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AMP) and Paclitaxel, Doxorubicin, Mitomycin C; CC-1065 and Paclitaxel, Doxorubicin, Mitomycin C; Trans-Resveratrol ((E)-3,5-dihydroxy stilben-3-ol) and Paclitaxel, Doxorubicin, Mitomycin C; Retinoic acid and Butyric acid; Paclitaxel and Doxorubicin; Doxorubicin and Biotin; 5-Fluorouracil and Cytarabine; Edatrexate and Paclitaxel; Cephalosporins and Paclitaxel; Cephalosporin and Paclitaxel; Levodopa and Carbidopa; Amoxicillin and Clavulanic acid; Ampicillin and Clavulanic acid; Amoxicillin and Penicillinic acid sulfonic; Oxivamic acid and 3-substituted Z-2-acylaminopyridine acid; Lofexidine and Lovastatin/Pravastatin/Fluvastatin/Atofvastalin/Sinivastatin; Ezetimibe and Lovastatin/Pravastatin/Fluvastatin/Atofvastalin/Sinivastatin; Metformin and Nateglinide/Glipizide/Glibenclamide (Glyburide); Metformin and Lovastatin/Pravastatin/Fluvastatin/Atofvastalin/Sinivastatin; Pseudoephedrine and Fexofenadine/Cetirizine/Hydroxyzine/Epinastine; Salbutamol and Ipratropium bromide; Mometasone and Fluticasone; Fluticasone and Fomoterol/Salmeterol; Diclofenac and Misoprostol; Diclofenac and Omeprazole/Esomeprazole/Lansoprazole/Pantoprazole; Naproxen and

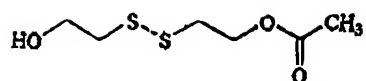
Prophenazone; Acetaminophen and chlorzoxazone/phenacetone; Zidovudine and Lamivudine; Triple prodrug of Zidovudine; Lamivudine and Abacavir (Ziagen); Lopinavir and Ritonavir; Lamivudine and Adefovir/didanosine; Amprenavir and Zidovudine; Nelfinavir and Zidovudine/Lamivudine; Stavudine and Zidovudine/Lamivudine; Dideoxyinosine and Zidovudine/Lamivudine; Emtricitabine and Didanosine; Acyclovir and Doxycycline/Chenodeoxycholate and Ursodeoxycholate; Triple and Zidovudine; and Lamivudine and Efavirenz.

19. A therapeutically effective amount of the pharmaceutical composition as in claim 15, comprising a two or three drugs, a drug and its own prodrug, a drug and a different prodrug, two different prodrugs, a drug and a mutual prodrug, mutual prodrug and its own drugs or a mutual prodrug and one of its constituent drugs.

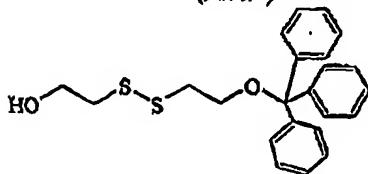
20. The compound according to claim 2, wherein D¹ and D² are therapeutic agents selected from the group consisting of: Sedatives, Hypnotics, Antidepressants, Antipsychotics and Antimanics, Analgesics, Antipyretics, Antimigraine agents, Anticonvulsants, Drugs used in parkinsonism and movement disorders, Drug for dementia, Antiemetics, drugs for Vertigo, CNS Stimulants activators; Antiinfective eye preparations; Antiinflammatory; antiallergic preparations, antiglaucoma drugs; preparations to cure eye diseases; aural, nasal and oropharyngeal preparation, Antianthelmintic drugs, Antihypertensives, alpha/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor antagonist^ diuretics. Antianginals* nitrates, calcium channel blocker^ Drugs for cardiac Mure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics, antiplatelet drugs, Respiratory stimulants, Antitussives, Expectorants, Mucolytics, Decongestants, Antihistamine agents, antihistaminic; Antiulcer, Antisecretory drugs, H₂ receptor antagonists, Proton Pump Inhibitors, Prostaglandin analogues, Antacids, Antispasmodics, drugs modifying intestinal motility, Antidiarrhoeals, antimotility drugs, antimicrobial drugs, drugs acting on gall bladder, Urinary antinfectives, Diuretics, Urinary analgesics, Antispasmodics, Antiinfective drugs acting on urethra and vagina, drugs acting on uterus, Drugs for prostatic hypertrophy, alpha blockers, antidiuretics, Drugs for erectile dysfunction, Spermicides, nonhormonal contraceptives, Emollients, keratolytics, topical antifungals, topical antiparasitics, topical steroids, topical drugs for acne vulgaris, drugs

- for psoriasis, pigmentation disorders, and Antiseboirrhoeics, Non Steroidal Anti Inflammatory Drugs (NSAIDs), COX-2 inhibitors, Anriarfhritic agents, Immunosuppressants, Topical analgesics, Muscle relaxants, Neuromuscular Drugs, Penicillin antibiotics, Cephalosporin antibiotics, Quinolone, Fluoroquinolone antibiotics,
- 5 MacroUde antibiotics, Chloramphenicol, Tetracycline antibiotics, Sulfonamides, Antiatiaerobics, Metronidazole, Antitubercular drugs, Antileprosy drugs, Antifungals, Antiprotozoals, Anthelminthics, Anti-infective Drugs, Antimalarials, Antivirals, Anabolics, androgenic steroids, Corticosteroids, Oestrogens, Progestogens and Hormonal contraceptives. Fertility Agents, Trophic hormones and related drugs, Thyroid and
- 10 antithyroid drugs, Antidiabetics and hyperglycemics, Vitamins, Amino acids, Anti-obesity drugs, Hypohypidaemic drugs, fibric acid derivatives, statins, HMG CoA reductase inhibitors* nicotinic acid group, drugs used for Gout, drugs affecting bone metabolism, bisphosphonates, Anticancer drugs, alkylating agents, cytotoxic antibiotics, antimetabolites, cytarabine, Fludarabine, 5-Fluorouracil, Mercaptopurine, Thioguanine,
- 15 Vinca alkaloids, Etoposide, Taxanes, Topoisomerase I inhibitors, Cytotoxic immunosuppressants, Immunostimulants, Cytoprotectives, Amifostine, Oestrogens, Progestogens, hormone antagonists, antineoplastic drugs, Antiallergics, non-sedative antihistamines, Cetirizine, Desloratadine, Terfenadine, Fexofenadine, sedative histamines, histamine receptor blockers, Local anaesthetics, intravenous anaesthetics, inhalation
- 20 anaesthetics, and muscle relaxants.
21. The compound according to claim 10 wherein D¹ and D² are from same or different therapeutic class and exhibit either the same or different mechanisms of action or work on same or different biological targets or work on same or different disease conditions.
- 25 22. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the composition according to claim 15.
23. A method of treating a mammal or human in need thereof comprising administering a therapeutically effective amount of the composition according to claim
- 30 16.

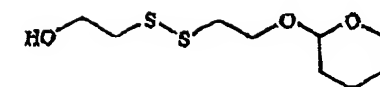
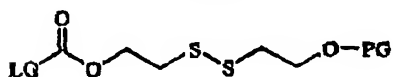
24. A method of use of the compound according to claim 2, for prevention or treatment of diseases where a chronic, sustained and selective release of the constituent drug or nitric oxide is beneficial.
- 5 25. A method of use of the compound according to claim 2, in a subject in need thereof for prevention or treatment of diseases of Central Nervous System, Eye, Ear, Nose and Oropharynx, Cardiovascular System, Respiratory System, Gastrointestinal tract system, Genito-urinary system, skin, musculoskeletal system, Endocrine system, metabolism and neoplastic disorders, infectious diseases, allergy and immunology, and for anaesthetic, analgesic and surgical needs.
- 10 26. A method of testing a mammal or human in need thereof comprising administering a therapeutically effective amount of two or more compositions according to claim 15, wherein compositions used in combination to treat a patient in need of a combination therapy.
- 15 27. A method of use of composition as claimed in claim 15, for prevention and/or treatment of diseases where a chronic sustained and selective release of the constituent drug(s) and/or nitric oxide is beneficial.
28. The novel intermediates obtained in the preparation of compounds of formula 1, wherein the intermediates are selected from:



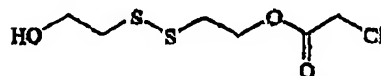
2-((2-Hydroxyethyl)disulfanyl)ethyl acetate
(LI-1a)



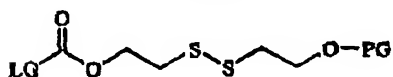
2-((2-(Trityloxy)ethyl)disulfanyl)ethanol
(LI-1c)



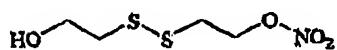
2-((2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)disulfanyl)ethanol (LI-1b)



2-((2-Hydroxyethyl)disulfanyl)ethyl
2-chloroacetate (LI-1d)



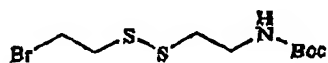
(LI-1xy)



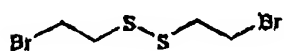
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2b)



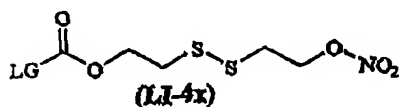
2-((2-Hydroxyethyl)disulfanyl)-
ethyl nitrate (LI-2c.TFA)



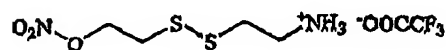
tert-Butyl 2-((2-bromoethyl)-
disulfanyl)ethyl carbamate (LI-2e)



1,2-Bis(2-bromoethyl)disulfane (LI-3a)



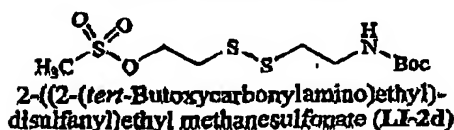
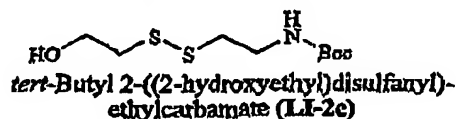
(LI-4x)



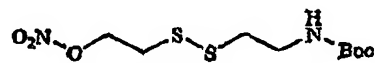
2-((2-Aminoethyl)disulfanyl)ethyl
nitrate, acid salt (LI-5.TFA)



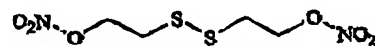
2-((2-Bromoethyl)disulfanyl)ethanol (LI-2a)



2-((2-(*tert*-Butoxycarbonylamino)ethyl)-
disulfanyl)ethyl methanesulfonate (LI-2d)



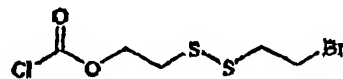
tert-Butyl 2-((2-(nitrooxy)ethyl)-
disulfanyl)ethyl carbamate (LI-2f)



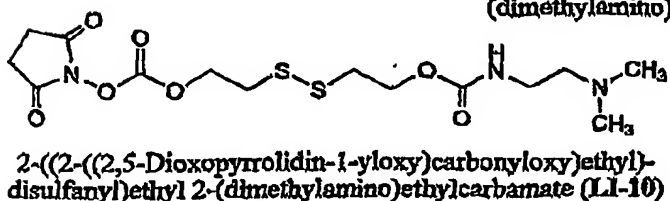
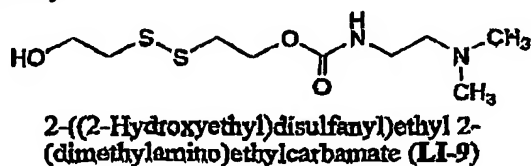
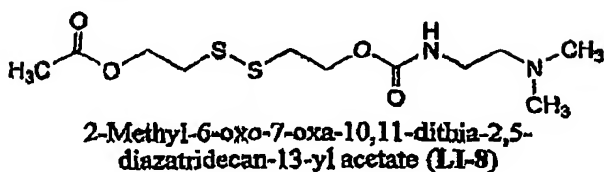
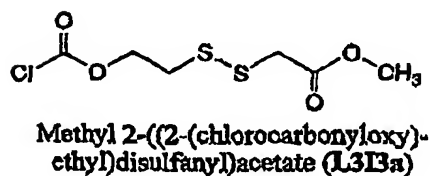
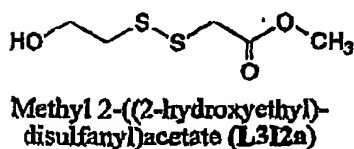
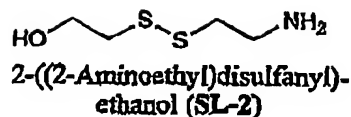
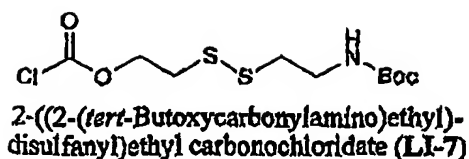
2,2'-Disulfanediyldis(ethane-2,1-diyl)
dinitrate (LI-3b)



2-((2-Aminoethyl)disulfanyl)ethyl nitrate (LI-5)



2-((2-Bromoethyl)disulfanyl)ethyl
carbonylchloride (LI-6)



29. The use of the novel intermediates of claim 28, in the preparation of compounds of formula i or pharmaceutically acceptable salts thereof,
- 5 30. The process for the preparation of the compounds of formula i or pharmaceutically acceptable salts thereof, wherein the process is selected from:
- Process 1: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-1) with an appropriate diacyl protecting group to give the corresponding monoprotected intermediate LMx,
- 10 B) Converting LMx, obtained in step A to an activated formyl intermediate LI-Ix by treating with phosgene or its equivalent, and

C) Reacting $J\Lambda xy$ obtained in the step B with an appropriate amino* or hydroxyl containing drug (D^1) to give the corresponding compound of formula I;

Process 2: A) Converting carboxyl containing drug (J^1) into its activated acyl halide or imidazolide or isocyanate by known methods, and

- 5 B) Reacting the intermediate obtained in the step A with the linker intermediate LI-Ix to obtain the compound of formula I;

Process 3: Mixing a selectively protected and activated drug with a solution of 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) in a suitable solvent in presence of a suitable coupling agent to obtain the compound of formula I and pharmaceutically acceptable salt

- 10 thereof, wherein D^2 is $NC\theta$

Process 4: Converting 2-((2-hydroxyethyl)dithio)ethyl nitrate (LI-2b) into its formyl halide or imidazolide (LI-4x) by using a phosgene or its equivalent reagent and mixing/reacting the resulting reactive intermediate with a suitable amino- or hydroxy-containing drug in suitable solvent in presence of a suitable base to obtain the compound

- 15 of formula I and pharmaceutically acceptable salt thereof, wherein D^a is NO^+ ;

Process 5: Mixing/Reacting an appropriately protected and activated drug with a solution of 2-((2-aminoethyl)dithio)ethyl nitrate (LI-5) in a suitable solvent in presence of a suitable coupling agent and/or base to obtain the compound of formula I and pharmaceutically acceptable salt thereof, wherein D^2 is NO_2 ; and

- 20 Process 6: A) Monoprotection of Bis-(2-hydroxyethyl)disulphide (SL-1) with an appropriate hydroxyl protecting group to give the corresponding monoprotected intermediate LMx,

B) Reacting formyl linker intermediate LIx with amino or hydroxyl containing drug (D^1) to obtain the prodrug of formula I with free hydroxyl group on the linker,

- 25 C) Converting the intermediate obtained in the step B into activated formyl halide or imidazolide derivative, and

D) Reacting the intermediate obtained in the step C with the drug P^2 to obtain the mutual prodrug of formula L

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 March 2006 (16.03.2006)

PCT

(10) International Publication Number
WO 2006/027711 A3

(51) International Patent Classification:
A61K 47/48 (2006.01)

(21) International Application Number:
PCT/IB2005/052797

(22) International Filing Date: 26 August 2005 (26.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/604,632 26 August 2004 (26.08.2004) US
779/MUM/2005 1 July 2005 (01.07.2005) IN

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US):
NICHOLAS PIRAMAL INDIA LIMITED [IN/IN];
Nicholas Piramal Research Centre, 1, Nirlon complex
Near NSE complex, (behind the Hub) Goregaon (East),
Mumbai 400 063 (IN).

(71) Applicant and

(72) Inventor: SATYAM, Apparao [US/IN]; Nicholas Piramal Research Centre, 1, Nirlon complex Near NSE complex, (behind the Hub) Goregaon (East), Mumbai 400 063 (IN).

(74) Agents: MAJUMDAR, S. et al.; S. Majumdar & CO, 5, Harish Mukherjee Road, Calcutta, 700 025 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report
- under Rule 91.1(f), with a request for rectification

(88) Date of publication of the international search report:
15 March 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PRODRUGS AND CODRUGS CONTAINING BIO-CLEAVABLE DISULFIDE LINKERS

(57) Abstract: The invention provides the compounds of formula (I) or pharmaceutically acceptable salts thereof. The invention also provides pharmaceutical compositions comprising one or more compounds of formula (I) or intermediates thereof and one more of pharmaceutically acceptable carriers, vehicles or diluents. The invention further provides methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula (I).

WO 2006/027711 A3

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2005/052797

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/040104 A (BIOTA SCIENTIFIC MANAGEMENT PTY LTD; JIN, BETTY; LAMBERT, JOHN, N; NEA) 15 May 2003 (2003-05-15) pag. 6 lines 7-12; pag. 45 structure 10 -----	1-3,20, 21
X	WO 2004/039771 A (DEPARTMENT OF SCIENCE AND TECHNOLOGY; TIWARI, MANISHA; SHARMA, MEENAKS) 13 May 2004 (2004-05-13) Comp. II pag. 4;	28
Y	-----	1-3, 14-16, 18-30
X	US 2003/044845 A1 (JENKINS THOMAS E ET AL) 6 March 2003 (2003-03-06)	1
Y	Abstract, Example A44 pag. 106 -----	1-3, 14-16, 18-30
	----- -/--	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 August 2006

Date of mailing of the international search report

118 DEC 2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bettio, Andrea

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2005/052797

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IGNARRO L J ET AL: "NITRIC OXIDE DONORS AND CARDIOVASCULAR AGENTS MODULATING THE BIOACTIVITY OF NITRIC OXIDE" CIRCULATION RESEARCH, GRUNE AND STRATTON, BALTIMORE, US, vol. 90, no. 1, 11 January 2002 (2002-01-11), pages 21-28, XP008051659 ISSN: 0009-7330 cited in the application	1
Y	Fig. 5 pag. 24	1-3, 14-16, 18-30
P,X	----- SHARMA M ET AL: "Bis[3-(4'-substituted phenyl)prop-2-ene]disulfides as a new class of antihyperlipidemic compounds" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 21, 1 November 2004 (2004-11-01), pages 5347-5350, XP004580528 ISSN: 0960-894X Pag. 5348 Scheme 1 comp. 6	28
Y	----- WO 2004/069159 A (ENDOCYTE, INC; VLAHOV, IONTCHO, RADOSLAVOV; LEAMON, CHRISTOPHER, PAUL;) 19 August 2004 (2004-08-19) Pag. 81 Example 37 and 38	1-3, 14-16, 18-30
Y	----- US 6 566 509 B1 (GRIFFIN JOHN H ET AL) 20 May 2003 (2003-05-20) Columns 45 structure X3; column 95 structure X 381	1-3, 14-16, 18-30
P,Y	----- US 2005/002942 A1 (VLAHOV IONTCHO R ET AL) 6 January 2005 (2005-01-06) cited in the application Example 37 pag. 60	1-3, 14-16, 18-30
Y	----- MAHGOUB H ET AL.: "Spectrophotometric determination of binary mixtures of pseudoephedrine with some H1-receptor antagonists using derivative ratio spectrum method" JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, vol. 31, 2003, pages 801-809, XP002393773 Abstract, pag. 802 last par.-pag 805 second column par. 2	1-3, 14-16, 18-30
A	----- WO 01/13957 A (CELLGATE, INC) 1 March 2001 (2001-03-01) Claim 73; Pag. 36 lines 24-31	1-3, 14-16, 18-30

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 14-16, 18-30 in part

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 22-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Although claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 17

The present claim 17 relates to an extremely large number of possible compounds. The non-compliance with the substantive provisions is to such an extent, that no search was performed (PCT guidelines 9.01).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Cetirizine, Desloratadine, Terfenadine and Fexofenadine and Pseudoephedrine; except for the subject matter of inventions 2-24

2. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Lisinopril, Losartan and Amlodipine; except for the subject matter of inventions 1, 3-24

3. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Celecoxib and Valdecoxib; except for the subject matter of inventions 1, 2, 4-24

4. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both selected independently from Fluoxetine and Olanzapine; except for the subject matter of inventions 1-3, 5-24

5. claims: 1-3, 11, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Gabapentin, Pregabalin, Vigabatrin, valproic acid, nicotinic acid, nicotinamide, Lamotrigine, Levetiracetam, Naproxen and Tramadol; except for the subject matter of inventions 1-4, 6-24

6. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Lamivudine and Zidovudine; except for the subject matter of inventions 1-5, 7-24

7. claims: 1-3, 14-16, 18-30 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Metronidazole and Norfloxacin; except for the subject matter of inventions 1-6, 8-24

8. claims: 1-3, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 and D2 are both independently selected from Venlafaxine and Paroxetine; except for the subject matter of inventions 1-7, 9-24

9. claims: 1-3, 15, 18-30 in part; claim 11 complete

Conjugates embraced by formula (I) of present claim 1 wherein D2 is a vitamin selected from the group consisting of vitamin A, vitamin C, thiamine, folic acid, biotin, inositol, riboflavin, pyridoxine, pyridoxal 5-phosphate, ergosterol, vitamin D2, vitamin D3, vitamin D4, vitamin E, menadoxime, menadiol, and vitamin K5; except for the subject matter of inventions 1-8, 10-24

10. claims: 1, 2, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is R2 and R2 independently represents H, NH₂, NHAc; except for the subject matter of inventions 1-19, 12-24

11. claims: 1, 2, 14-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is R2 and R2 independently represents COR₅ or CH₂CO₂R₅ and wherein R₅ is defined as in present claim 1; except for the subject matter of inventions 1-10, 12-24

12. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is R4 and R4 represents one of the groups defined in present claim 1 except H, amino-functionalised water soluble polymers and except amino-modified dextran or arabinogalactan; except for the subject matter of inventions 1-11, 13-24

13. claims: 1, 2, 12-16, 18-30 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Gabapentin, Pregabalin, Vigabatrin, valproic acid, nicotinic acid, nicotinamide, Levetiracetam, Lamotrigine and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-12, 14-24

14. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Lisinopril, Hydralazine, Amlodipine and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-13, 15-24

15. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Omeprazole, Metronidazole and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-14, 16-24

16. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Valdecoxib and Celecoxib and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-15, 17-24

17. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Paracetamol and Aspirin and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-16, 18-24

18. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is 1-hydroxy-TEMPO and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-17, 19-24

19. claims: 1, 2, 12-16, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D1 is Budenoside and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-18, 20-24

20. claims: 1, 2, 12-16, 18-30 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates embraced by formula (I) of present claim 1 wherein D1 is selected from Naproxen, Flurbiprofen, Indomethacin, Ketoprofen, Diclofenac and D2 is NO, NO2 or NONOate; except for the subject matter of inventions 1-19, 21-24

21. claims: 1, 2, 5-9, 15, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is a polymer selected among dextran, modified dextran and arabinogalactan; except for the subject matter of inventions 1-20, 22-24

22. claims: 1, 2, 5-9, 15, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is a polyaminoacid; except for the subject matter of inventions 1-21, 23, 24

23. claims: 1, 2, 5-9, 15, 18-30 in part

Conjugates embraced by formula (I) of present claim 1 wherein D2 is polyethylene glycole (PEG); except for the subject matter of inventions 1-22, 24

24. claims: 1, 2, 15, 18-30 in part 4; 10 complete

Conjugates embraced by formula (I) of present claim 1 wherein D2 is an amino acid selected among those disclosed in present claim 4 or a dipeptide; except for the subject matter of inventions 1-23

INTERNATIONAL SEARCH REPORT

 International application No
 PCT/IB2005/052797

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03040104	A	15-05-2003	US	2005085413 A1	21-04-2005
WO 2004039771	A	13-05-2004	AU	2003247161 A1	25-05-2004
US 2003044845	A1	06-03-2003	NONE		
WO 2004069159	A	19-08-2004	AU	2004210136 A1	19-08-2004
			CA	2512867 A1	19-08-2004
			EP	1592457 A2	09-11-2005
			JP	2006518712 T	17-08-2006
US 6566509	B1	20-05-2003	US	2003176670 A1	18-09-2003
US 2005002942	A1	06-01-2005	NONE		
WO 0113957	A	01-03-2001	AU	769315 B2	22-01-2004
			AU	6939400 A	19-03-2001
			CA	2381425 A1	01-03-2001
			EP	1210121 A2	05-06-2002
			JP	2003507438 T	25-02-2003
			MX	PA02001857 A	14-07-2003